

# **ROLE OF LOCOREGIONAL TREATMENT IN THE MANAGEMENT OF METASTATIC BREAST CANCER**

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## **AIM OF THE STUDY:**

Aim of this retrospective study is to evaluate the role of loco regional treatment such as local radiotherapy and surgery in the management of patient with metastatic breast cancer.

## **MATERIALS AND METHODS:**

One hundred and Ninety five patients with metastatic breast cancer between the years 2003 to 2008 were taken for this retrospective study. Among these, seventy five patients did not receive locoregional treatment, and the remaining one hundred and twenty patients received locoregional treatment to the primary. Locoregional treatment included radiotherapy and surgery.

## **RESULTS:**

Patients survival was analyzed at the end of 1 year, 3 years, 5 years, and at the end of 10 years. It was found that, in patients receiving concurrent chemoradiation, survival at the end of 1, 3, 5 and 10 years were 89%, 58%, 46% and 42% respectively. Similarly, in patients receiving concurrent chemoradiation followed by surgery, survival was 97%, 80%, 71% and 70% respectively. Further,

survival for chemotherapy was 60%, 5%, 2% and 0% respectively. Again, for the arm including only radiotherapy, survival was around 67%, 33%, 33% and 33% respectively. Those patients who receive only hormonal therapy had 50%, 13%, 13% and 13% overall survival at the end of 1, 3, 5 and 10 years.

### **CONCLUSION:**

The data reported in this retrospective study confirmed that chemo-radiation improved overall survival and symptomatic local control, demonstrated in loco-regionally treated patients with metastatic breast cancer.

## **INTRODUCTION**

### Evolution of breast cancer

As carcinoma of breast has no clear cause hence gained much attention throughout the ages all over the world. The story of breast cancer is complex as there is no happy ending unlike other diseases. The development and milestones of breast cancer started from the ancient civilization of the Chinese, Egyptian, Babylonian, Greek, Greco-Roman, middle ages Christian, Jewish, Arabic.

The Chinese form of medicine describes five forms of therapy for tumors.

1. Spiritual care
2. Pharmacology
3. Diet
4. Acupuncture
5. Treatment of specific diseases

Egyptian form of medicine was described by IMHOTEP who used cautery for cancer. Edwin Smith during his period obtained information from Papyrous roll described that breast cancer that are cold on touch has no treatment.

During Greek period, Hippocrates described diseases in three groups.

Curable when medicine

1. Curable by knife
2. Curable by fire

Hippocrates also described that breast cancer was the cessation of menstruation.

Greco-Roman period – Aurelius Celsus described breast cancer as a fixed irregular swelling with dilated veins and ulcers and divided into four staged

1. Early cancer
2. Cancer without ulcer
3. Cancer with ulceration
4. Cancer with cauliflower like growth, and advised no treatment for last three stages.

The first physician who operated breast cancer in the first century was LEONIDES. His method of surgery was by using incision from the uninvolved part of the breast and applied cautery to stop bleeding, the same method was repeated until the whole breast is removed and the underlying tissue was covered with eschar. Galen described breast cancer was due to black bile and said breast cancer looks like a crabs leg and suggested patient to be purged and bleed and to let out the tumor in early stages.

From Middle Ages – downfall of Romans – beginning of Renaissance - Christian

During this period the patron of breast disease was Saint Agatha in the third century whose breast was cut off using sheets

Arabic Rhazes advised excision of breast cancer only if it was completely operable. Hay ben Abbas advised complete excision of the disease and allowed bleeding to evacuate the bad disease.

Renaissance – from medieval to modern Era

Andreas Vesalius recommended mastectomy for breast cancer and used sutures instead of cautery. Ambrose Pare described lymph node metastases of breast cancer. Servetus described the method of removal of pectoralis muscle with axillary glands. Wilhelm Fabry, father of German surgery compressed and fixed the base of breast and used knife to amputate the breast. Johan Schultles, German surgeon, inventor of surgical instruments .18<sup>th</sup> Century

Henri Le Dran of France described carcinoma of breast as a localized disease in early stages and lymph nodal spread as bad disease with bad prognosis. Jean Petit, friend of Le dran advised surgery of breast cancer involves removal of breast, pectoral muscles and axillary nodes. German surgeons, Lorez and Heister advised Guillotine machine for breast tumor.

Heister described the relationship between surgeon and patient and said that surgeons should be steady and not to be disconnected by the cries of the patient.

19<sup>th</sup> Century- period of invention of anaesthesia and antisepsis hence breast cancer surgery improved.

European surgery –

Nooth an English surgeon sprayed carbolic acid over the breast instead of cautery. Syme described the need for axillary lymph node dissection in breast cancer patients. Charles Moore believed in extensive surgery for breast cancer and said that tumor should not be cut as it may disperse the tumor and allow recurrence of the disease. He also advised the entire removal of breast with skin and not to remove pectoralis muscle. Richard Van Volkman advised extensive surgery even for small tumors. Theodor Billroth also advised the same. Ernst Kuster advised removal of axillary fat with axillary nodes. Lothar Heidenhain advised removal of superficial pectoralis major muscle. Everard Home showed appearance of cancer cells under microscope. Henrich Van WaldeyerHantz described carcinoma arising from epithelial tissue and

sarcoma from mesodermal tissue. Victor Cornil described malignant transformation of acinar epithelium of breast. David Van Hanseman described differentiation of cancer cells (ANAPLASIA)

#### American Surgery

Joseph Pancoast described the pre-anesthetic era of mastectomy with axillary lymphatic drainage. Samuel D. Gross described breast conservation surgery. William Halsted advised removal of breast cancer with pectoralis muscle. William Meyer modification of Halsted's procedure advocated removal of pectoralis minor muscle along with pectoralis major. Cullen and William Welch was the first to do the frozen section of the breast in the diagnosis of breast cancer.

20<sup>th</sup> century it became evident that cure can be achieved by surgery. Halsted and Meyer surgery didn't include supra clavicular and internal mammary nodes and its removal did not show any improvement in survival. William Handley showed the involvement of internal mammary node when axillary node was involved in breast cancer patients. Jerome and Owen Wangsteen advised supra radical Mastectomy which involved dissection of mediastinum and neck.



Cushman Haagensen classified breast cancer according to size and nodal status . He was the first person to advise breast self-examination. In 1948 the first concept of modified radical mastectomy was done by Patey and Dyson. Donald Morton and Giuliano developed sentinel node biopsy technique. In 1937 London surgeon, Geoffrey Keynes described minimal surgery for breast cancer and advised radiotherapy which had equally good result . In 1948 simple Mastectomy followed by radiotherapy was introduced by R. McWhirter.

## **Radiotherapy**

Emile Grubbe medical graduate studying 2<sup>nd</sup> year from Chicago was the 1<sup>st</sup> person to irradiate breast cancer patients, he used tin foil to protect the normal skin to protect the normal skin

In 1896 Hermann Gocht of Germany treated breast cancer patients with radiation and used flexible lead to protect normal tissue

In 1903 1<sup>st</sup> department of radiotherapy was founded by J. Pollock in London George Perthes a surgeon from Germany described curative effect of X-rays

Post op radiotherapy was used in America and Europe before world war I. before world war I energy used was 150kv X-rays, after world war II 170-200kv X-rays was used

In 1929 S. Harrington of the Mayo Clinic studied 1859 breast cancer patients irradiated between 1910-1923. He expressed doubts about ancillary RT George Pfahler from Philadelphia advised post op RT

for all cases of breast cancer after 2 weeks of surgery. In his review of 102 patients there is no significant benefit in survival in stage I patients but showed a improved 5 year survival in stage II patients.

Radiotherapy as a single modality for breast cancer was used in inoperable cases during the beginning of 20<sup>th</sup> century until 1922.

William Stone from New York showed the benefit of RT over surgery in inoperable breast cancer based on his experience on 10000 patients.

Geoffrey Keynes from London in 1932 used radium for therapeutic use irradiation and showed 5 years survival rate of 77% in node negative patients and 36% with node positive patients.

1930 super voltage X-rays were available .Francois Baclesse of Paris did local excision of breast cancer followed by RT from 1937-1953, and said that results were equal for stage I and stage II breast cancer , between post op RT vs only surgery.

In 1948 Robert McWhirter proposed simple mastectomy followed by RT. He said radical mastectomy was overkill for stage I breast cancer, but inadequate for stage II breast cancer.

1960 cobalt emerged

1970 linear accelerator emerged

## **Chemotherapy**

Paul Ehrlich was the father of chemotherapy. Arsenic was used in ancient times for breast cancer treatment.

- 1898 1<sup>st</sup> alkylating agent was used.
- World war II nitrogen mustard came into use .
- 1957 C. Heidel Berger used 5FU in breast cancer.
- In 1958 thiotriethylenephosphamide alkylating agent.
- 1963 E. Greens Span used multi drug trials using methotrexate with thiotepa.
- Gianni Bonadona was the 1<sup>st</sup> person to start CMF regimen in breast cancer.

## **Hormone therapy**

Hormone therapy in breast cancer patients was started even before 20<sup>th</sup> century in 1889- Schinzinger of Germany proposed oophorectomy before mastectomy .

In 1896-1901 George Beatson advised oophorectomy for breast cancer patients .

In 1900 Boyd was the 1<sup>st</sup> person to combine oophorectomy with mastectomy.

In 1953 Charles Hignnes combined oophorectomy and adrenalectomy .

In 1950s hypophysectomy was done for advanced breast cancer.

1939 P.Ulrich used testosterone for breast cancer .

In 1944 Alexander Haddow used synthetic oestrogen .

In 1938 Edward Dodds synthesized stilbesterol.

I.Naphasyn also synthesized stilbesterol .

In 1950-1960 oestrogen and androgens was used much.

In 1973 W.McGuire demonstrated oestrogen receptors in breast cancer patients .

In 1975 K.Horowitz demonstrated progesterone receptors.

In 1980 tamoxifen and SERM was used

## **History of staging**

Has a long history surgeons divided into two groups to decide on surgery either inoperable or operable, on the basis of certain observations staging was initiated .

Steinthal's grouping

Group1

Group 2

Group3

In 1940 manchester classification consists of

stageI

stage II

stage III

stage IV

Portmann classification

In 1943 CCC(columbia clinical classification )evolved from  
Haagensen and Stout's

Stage A-D



In 1954 UICC emerged started TNM classification developed by Pierre Denoix of France

In 1962 AJCC emerged .Carcinoma breast is the most commonly diagnosed cancer in women all over the world, affecting nearly 21% of all cancer diagnosed in females a with high ratios in North America, Western Europe, intermediate rates in South America and Eastern Europe and low rates in Asia. 10 percent of newly diagnosed breast cancer patients have metastatic breast cancer. After all treatments nearly one third of patients will have progressive disease . metastatic breast cancer median survival for the 3 yrs.

The range is very wide with some patients having more indolent disease that they can live upto 10 – 15 years, while for others with disseminated metastatic disease, the prognosis will be in the range of months from the time of diagnosis. This will represent the disease extent and distribution of metastatic disease, and reflects the biological behaviuor of carcinoma of breast, while some women have disease which shows good response to hormonal treatments, while others with triple negative breast cancer can show increased resistance to all systemic therapies.

The aim of treatment breast cancer is to increase the symptom free survival and increase quality of life . at the same time the side effect of the treatment to be minimised. The treatment for metastatic breast cancer is depends on the individual patient and receptor status, general condition of the patient. Even with newer systemic and locoregional treatment metastatic breast cancer cannot be cured at present. In few patients with good prognostic factor these treatment modalities increase the progression free survival which in turn may significantly affect the overall survival. Many patients with metastases may live several years with modern locoregional treatment and systemic chemotherapy.

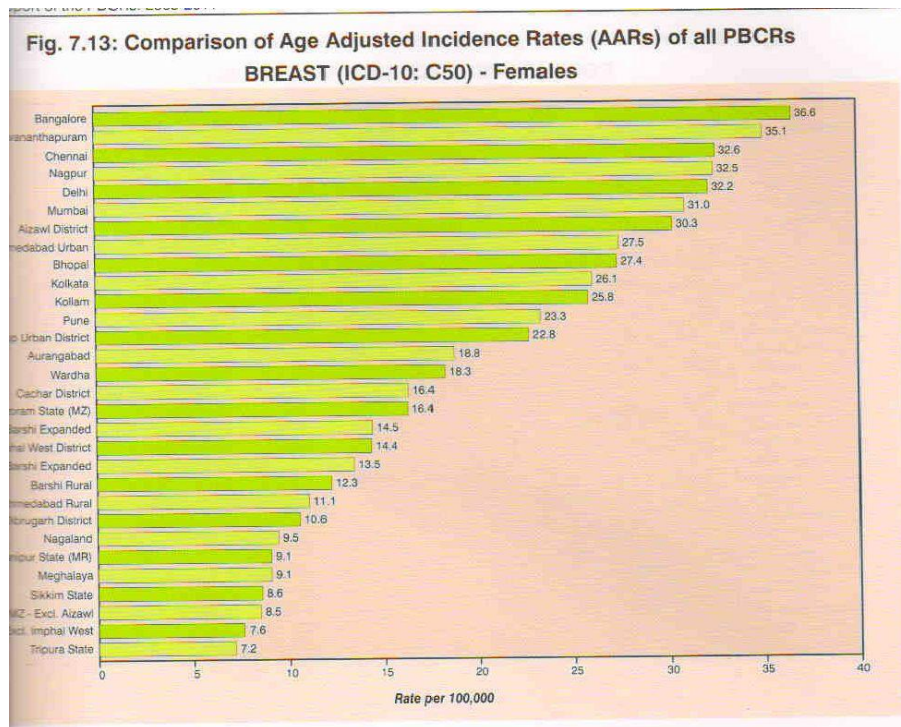
Breast Cancer Statistics

Regions	No.of Cases	CIR	ASR
World	1676633	47.9	43.3
More Developed Region	793684	124.1	74.1
Less Developed Region	882949	30.9	31.3
India	144937	23.8	25.8
Chennai (09-10)	1568	34.2	35.7

CIR: Crude Incidence Rate per 100000 Populations

Source: Globocan 2012, IARC Publications & MMTR Report

**TOTAL NO OF BREAST CASES IN CHENNAI IN THE YEAR OF  
2012 - 1568**



## NATURAL HISTORY AND ORIGINS

Concepts regarding the natural history of breast cancer have undergone great evolution over the past 100 years, with a profound impact on the management of these patients. The Halsted model was based on an orderly progression to the regional lymph nodes and from there to distant metastatic sites. Later another hypothesis was fully demonstrated in both laboratory and clinical studies by Fisher, who advanced the concept that breast cancer, as a systemic process involving

host–tumor interactions, would not show substantial effects on survival with variations in locoregional treatment.

A third hypothesis put forward by Hellman considers breast cancer as a heterogeneous disease with a spectrum extending from a tumor that remains localized throughout its course to one that disseminates systemically, even when detected as a small lesion, suggesting that metastases are a function of tumor growth and progression factors.

## **BREAST CANCER RISK FACTORS**

Established Risk factors,

1. Age of the patient

Early Menarche, late menopause, Age at first child birth( related to estrogen exposure)

1. Duration of Breast feeding

Decreasing the breast cancer risk by delaying ovulation and decreasing the hormone exposure

2. Height weight and body mass index

3. Physical activity
4. Alcohol consumption
5. High dose estrogen containing oral contraceptive pills  
And hormone replacement therapy in postmenopausal women
6. Ionizing Radiation
7. Family history and genetic susceptibility

#### Possible risk factor

1. Fat and future
  2. Dietary phytoestrogen
- Hereditary breast cancer

5-10% of the breast cancer is due to familial risk factor.

The breast cancer susceptibility genes divided into three types.

1. High penetrance
2. Intermediate penetrance
3. Low penetrance

Low penetrance are the most common variety BRCA1 and BRCA2 genes Fifty percent of the familial breast cancers are mainly due to BRCA1 and BRCA2 genes.

This increases the relative risk of the cancer breast to 10 to 30 times of the normal population.

The prevalence is more common in jewish population. BRCA1 mutations characteristically has a basal – like phenotype, inactivating germiline mutation. The similarity between hereditary BRCA1-related sporadic BLBC sporadic basal like breast cancers may also harbor an underlying defect in BRCA1, which has been termed “BRCAness”. BRCA2 – related cancers do not have an association with TNBC or the basal – like phenotype. Other rare breast cancer susceptibility genes related to the breast cancer are CHEK2,TP53,PTEN,STK11

## **DISTIBUTION**

Upper outer quadrant is the most common site of carcinoma breast which contributes about 38% of the total incidence. The second common site is the central area of the breast followed by upper inner quadrant and then the lower inner quadrant.

The distribution correlates with the difference in density of breast tissue in various quadrants.

## **LOCAL SPREAD**

During the development and progression of the breast carcinoma, it starts from the ducts and then breaches the basement membrane enters into the surrounding breast parenchymal structure. The tumor can grow through the wall of blood vessels, spread into the deep lymphatics of the dermis, and eventually produce edema of the skin (*peaud'orange*), which usually indicates that the superficial as well as the deep lymphatics are involved. Skin dimpling can be caused by involvement of Cooper's ligament. Ulceration and infiltration of overlying skin, which may

develop late in the course of the disease, are usually preceded by fixation and localized redness of the skin over the tumour.

### **Axillary Spread**

Majority of the breast carcinoma spread through axillary nodes and the percentage of the nodal involvement increases with tumour size. The percentage varies from between 10% and 40% depending on the size of the tumour.

### ***Supraclavicular Spread***

Spread to supraclavicular lymph nodes usually follows involvement in the high axillary lymph nodes or IMNs. Clinical failure in the supraclavicular fossa is relatively rare in patients with early-stage breast cancer and is dependent on the degree of axillary involvement. For patients with no or minimal nodal involvement (less than three involved axillary nodes), supraclavicular failure is extremely rare.



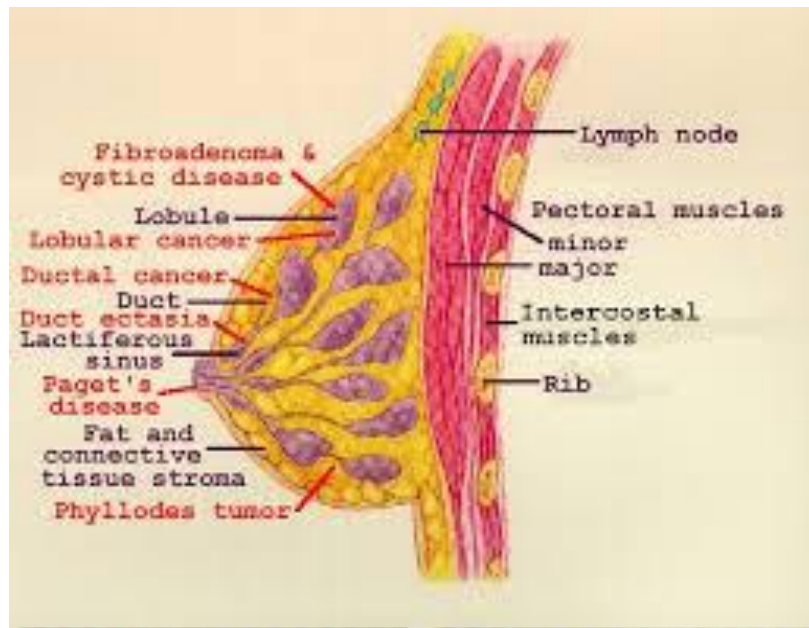
### ***Internal Mammary Spread***

Metastases to the internal mammary nodes (IMNs) are correlated with tumour size, are more frequent from medial half and central lesions, and occur more frequently when there is axillary node involvement

### ***Systemic Spread***

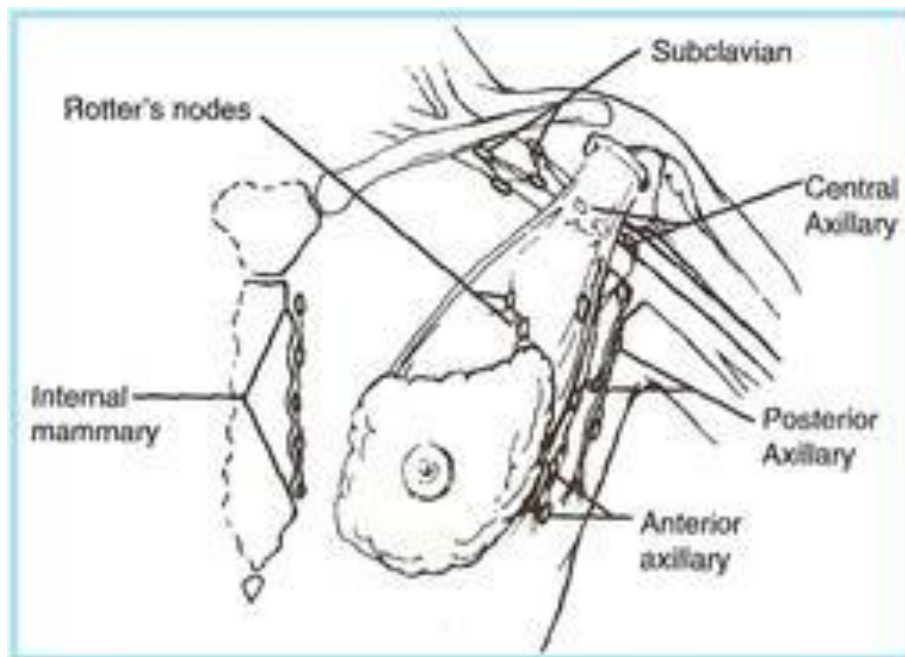
- Of the systemic metastasis,
- Approximately 60% are in bone,
- 10% in lungs, 5% in liver,
- 5% in central nervous system
- 15 to 20% in multiple sites.

### **ANATOMY**

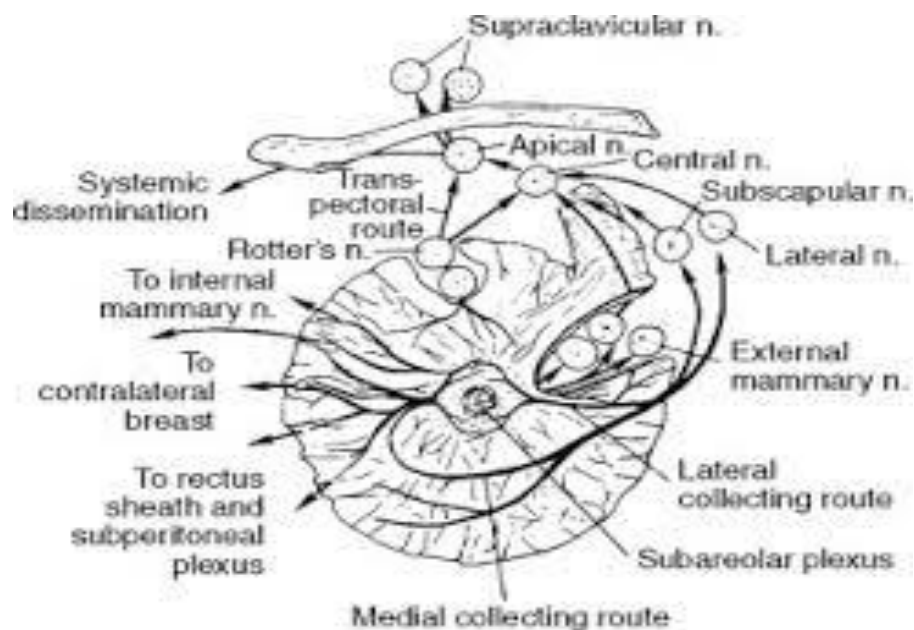


The female breasts are modified eccrine glands on the anterior chest wall, superiorly from the second rib to inferiorly up to the 6<sup>th</sup> rib, medially to the sternal edge and laterally up to the mid axillary line. The breast parenchyma is composed of lobules and ducts. The function of the lobules is to produce milk and the function of the ducts is to transport lactation products to the nipple. The breast parenchyma is intermixed with connective tissue, which has a rich vascular and lymphatic network. Mammary gland lymphatics begin in the interlobular or prelobular spaces, follow the ducts, and end in the sub areolar network of lymphatics of the skin.

#### Lymphatic drainage of the breast



The predominant lymphatic drainage of the breast is to axillary lymph nodes. The level I axilla is caudal and lateral to the muscle, level II is beneath the muscle, and level III is cranial and medial to the muscle. Lymphatics can also drain directly into the internal mammary lymph node chain (IMC), which are intrathoracic structures located in the parasternal space. Although these nodes are not usually visualized on computed tomography (CT), the anatomical region of the IMC can be determined by the internal mammary artery and vein, which are easily visualized by CT (Fig. 56.3) and usually lie 3 to 4 cm lateral to midline.



## **PATHOLOGY**

Breast carcinomas are divided into insitu carcinoma and invasive carcinoma

Insitu carcinoma are divided into ductal carcinoma insitu and lobular carcinoma insitu.

## **INVASIVE CARCINOMAS**

The histological typing of breast cancer is made by exclusion  
INVASIVE DUCTAL CARCINOMA (NOS) is an invasive carcinoma that doesn't fulfil definition of other categories.

Invasive lobular carcinoma, tubular carcinoma, mucinous carcinoma, cribriform carcinoma, papillary carcinoma, scirrhous carcinoma, comedo and medullary carcinomas are few specified types of breast carcinoma. Histological used in the Breast cancer is proposed by elston and ellis it is the modification of bloom rich at son in 1957 it has 3 factors

1. Tubule formation
2. Pleomorphism
3. Mitotic activity

Each factor scored on a scale of 1-3 tubule formation Histological grade

3 – 5 - well differentiated tumours

6 – 7 - moderately differentiated

8 – 9 - poorly differentiated

### **Luminal A**

100% ER positive, 70% PR positive, good risk , 10 years relapse free survival 70%, low risk on oncotype Dx and Mamma print and hormone responsive tamoxifene responsive , chemo insensitive , Ki 67% <14% primary tumor 62% T1 , 38% T2 , HER2 negative ,

### **Luminal B**

ER positive less than 50%, PR positive bad prognosis , 10 years relapse free survival 53% , tamoxifene insensitive , aromatase inhibitor sensitive , Ki 67% more than 14% , younger age higher grade , 30% are

HER2 positive ,Intermediate to high risk on oncotype DX and Mamma print

### **Basal type**

Do not express ER,PR or HER2 negative 85% (triple negative) are basal

Express myoepithelial cell membrane CK5 , C-Kit ,EGFR, HER2 tends to be high grade .

NG-III, present with large tumours T2 and above chemoresponsive high relapse rate in CNS

**BRCA1 tend to be basal line common in African Americans**

### **Angiogenesis**

Targeting angiogenesis in metastatic breast cancer Judah Folkman in 1970 first described the concept of angiogenesis by targeting blood vessel formation by preventing tumour growth and metastasis . he defined anti angiogenesis therapy which causes regression of tumour by altering tumour vasculature , normalization of surviving tumour vasculature , inhibition of regrowth of vessel and neovascularisation in

tumours, eg. antiVEGF antibody-Bevacizumab dose:10mg /kg every 2weeks of 15mg /kg every 3weeks

Prognostic bio marker

Indicates the probability of specific clinical outcome such as recurrence progression survival independent of treatment

Predictive bio marker

Indicates the chance of response to specific therapy

Response indicator

Monitors response and assist in stop vs continue treatment

Pharmacokinetic bio marker

It measures pharmacokinetic parameters of drug exposure

Pharmacodynamic bio marker

Measures end point of drug effect on target pathway and downstream biological process

Prognostic multigenes signatures in carcinoma breast

Mamma print –microarray-70genes –freshfrozen tissue

Rotterdam signature-microarray-76 genes-freshfrozen tissue

Genomic grade index-microarray-97genes-freshfrozen tissue

Mammostrat IHC-5genes-Formaline embedded fixed paraffin

Oncotype DX –qRT-PCR-21 genes- Formaline embedded  
fixed paraffin

## **DIAGNOSTIC EVALUATION**

### **History**

Complaints related to the breast cancer and history related to the risk factors to be elicited history of any lump in the breast, nipple discharge, skin changes, any axillary swellings to be asked.

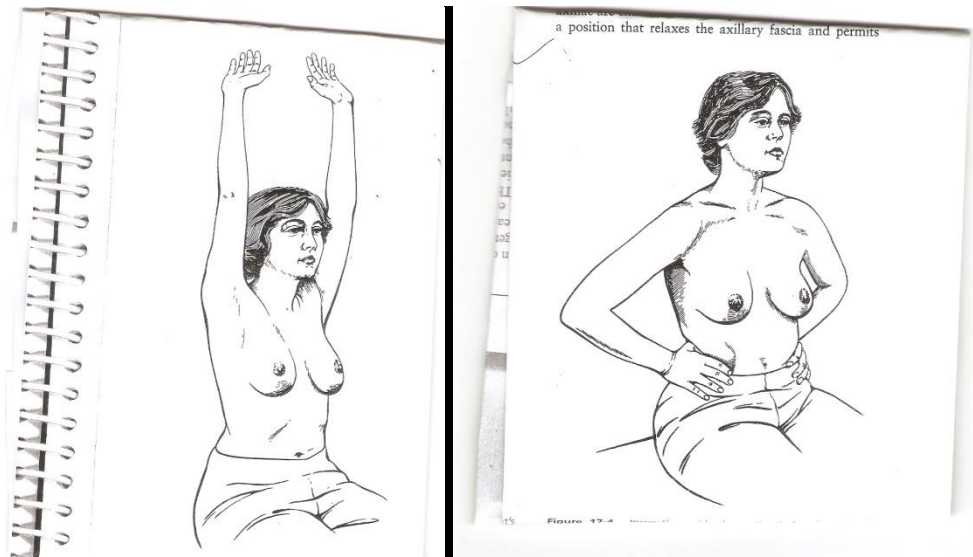
### **Physical examination**

It includes inspection and palpation of the breasts, axilla, supraclavicular region,

The breast is examined by various positions including sitting with arms either side, sitting positions with arms above the patient's head, patient's hands pressed against her hips the following changes in the breast to be noted

1. Any asymmetry of the breast
2. Inverted nipple
3. Skin changes



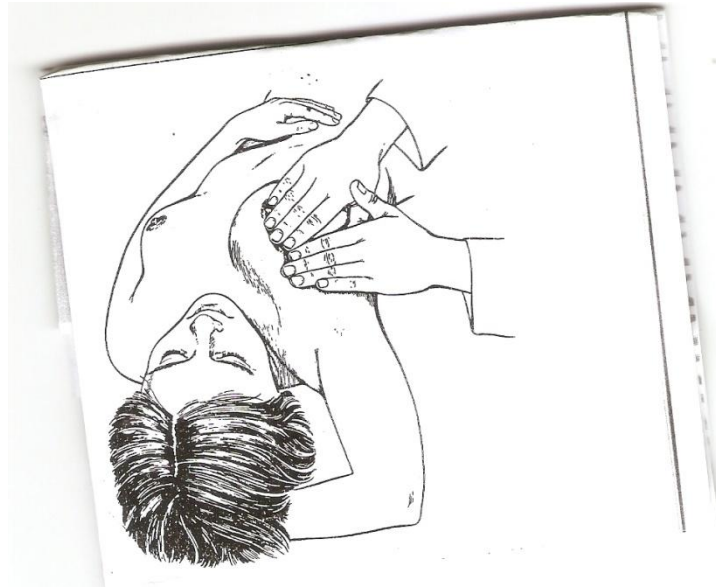


Palpation of breast.

It should be performed with the patients in supine position and also in sitting position

Signs of breast cancer.

1. Palpable mass
2. Nipple discharge- unilateral bloody discharge
3. Nipple changes – any retraction, infiltration, pagets .
4. Skin changes – dimpling or skin retraction.



## **Biopsy**

The following important factors to be identified in the specimen which is needed for further management.

Hormone receptor status – ER,PR status

1. HER2 neu status
2. Histological type of cancer
3. Histological grading

Baseline investigations

1. Complete blood count
2. Blood biochemistry
3. Liver function test

4. Renal function test
5. X ray chest PA view
6. Ultrasound abdomen and pelvis
7. Ct chest
8. Bilateral mammogram.

## **MAMMOGRAM**

Mammogram provides additional information

In the presence of palperable mass mammography is useful in detecting occult lesion in same or opposite breast, it is classified as screening mammography of diagnostic mammography

Screening mammography to screen asymptomatic women  
Diagnostic mammography is a definite imaging workup to locate a mammographically visible lesion

## **IMPORTANCE OF MAMMOGRAPHY IN BREAST CANCER**

Reduction in breast mortality

Swedish country trial 30% (40-74 years)

Malmo trial 36% (45-49 years)

Gottenberg trial 45% (39-49 years)

Metaanalysis of 5 swedish trials 29% (40-59 years)

## **TYPE OF VIEWS**

In screening mammography –two views, mediolateral oblique view and cranio caudal view

In diagnostic mammography – mediolateral view craniocaudal view and exaggerated CCL –CCM

## **MAGNIFICATION VIEWS**

BI-RADS ( british imaging reporting and data system) false negative 75-80% due to dense breast in young women

### **Classification**

Category 0 – assessment incomplete used in screening

Category 1 – normal

Category 2 – benign finding

Category 3 – benign probably

Category 4 – malignancy suspected

Category 5 – malignant

What is triple diagnosis?

Physical finding

FNAC

### **Mammogram**

## **WHAT IS A MASS?**

M –mobility	T – tenderness
A –attachement	L - location
S –shape	C - consistency
S – size	

## **DEFINED AS A PALPABLE ABNORMALITY DISTINCT FROM SURROUNDING TISSUE**

### **USG of breast**

USG of breast is a useful complement to mammography for evaluation of dense breast when results of physical examination and mammography are equivocal useful in these group of patients

1. Those with dense breast and localized symptoms of with a suspicious area detected in MMG
2. Those with non palpable abnormality discovered on MMG
3. Those with palpable masses considered intermediate on MMG
4. To guide aspiration of non palpable cystic structure
5. To do FNAC of small lumps

## **MRI of breast**

Sensitivity 97-99%

Specificity 28-37%

Greatest strength of MRI to detect occult metastasis in dense breast and recurrence after irradiation

FDG PET scan

Sensitivity 93%

Specificity 73%

Accuracy 89%

Positive predictive value 92%

Negative predictive value 96%

False negative 20%

Bone scan: technetium 99, F18 – more specific recommended for stage II and above cancers and T size >2cm

The mammographic findings for malignancy include ill defined mass with spiculations, micro calcifications (100 to 300 um rod like, tubular, branching or punctuate) and architectural distortion.

Magnetic Resonance Imaging

## **Indications**

- To assess the silicone implant integrity
- To diagnose the malignancy in reconstructed breast
- To rule out multifocal disease before doing Breast reconstructive surgery
- To assess the response to neoadjuvant chemotherapy
- To diagnose the occult primary.

Positron Emission tomography The metabolism of the tumour cells are mainly by glycolysis not by oxidative metabolism

This difference between tumor cells and normal cells is the basis for the PET imaging.

## **Uses**

1. To differentiate the recurrent breast cancer from postoperative scar.
2. Have high accuracy in detecting presence or absence of lymph node involvement

3. Able to screen the whole body in a single imaging method for distant metastasis
4. Pet is very much useful in the quantitative response assessment after neoadjuvant chemotherapy.

### **STAGING (TNM CLASSIFICATION) AJCC 2010**

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1 mic	Tumor $\leq 1$ in greatest dimension
T1a	Tumor $> 1 < 5$ mm in greatest dimension
T1b	Tumor $> 5 < 10$ mm in greatest dimension
T1c	Tumor $> 10 < 20$ mm in greatest dimension
T2	$> 2 < 5$ cm in greatest dimension



T3	>5cm in greatest dimension
T4a	Extension to chest wall not including pectoralis muscle
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d' orange) of the skin
T4c	Both T4 a and T4b
T4d	Inflammatory carcinoma
Nx	Regional lymph nodes cannot be assessed
No	No regional lymph nodes
N1	Metastases to movable ipsilateral axillary lymphnodes(s)
N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node

	metastases
N3a	Metastases in ipsilateralinfraclavicular lymph node (s)
N3b	Metastases in ipsilateral internal mammary lymph nodes (s) and axillary lymph node (s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
M0	No distant metastasis
M1	Presence of distant metastasis

## COMPOSITE STAGING

STAGE 0	Tis No Mo
STAGE1A	T1 No Mo
STAGE1B	To N1 mic Mo
STAGE2A	T1 N1 mic Mo
STAGE2B	T0 N1Mo, T1 N 1 Mo, T2 No Mo

STAGE3A	T0N2M0, T1 N2 M0, T2 N2 M0 T3 N1 M0, T3 N2 M0
STAGE3B	T4 N0 M0, T3 N1 M0 T4 N2 M0
STAGE3C	Any T N3 M0
STAGE4	Any T Any NM1

Overall survival of breast cancer patients correlates with the stage of disease at presentation. The table depicts 5 years survival according to stage of the disease”

Stage	5 Year Survival
0	100%
1	98%
2A	88%
2B	76%
3A	56%
3B/C	49%
4	16%

## **METASTASES:**

The metastatic potency of cancer cells depends upon the intrinsic properties of tumor and their interactions with tissue environment. The steps of metastases include Proliferation of tumor cells by paracrine growth (tissue environment), autocrine growth (from tumor itself)- EGFR, c-erb /HER2neu, TGF- alpha, HRG, Neovascularisation due to new vessel formation by factors released by the tumor and tumor cells exhibit motility there by detachment and movement from the primary site

Invasion is a process by which there is destruction of basement membrane, connective tissues, adhesion and motility with response to release of factors. Distant metastases is due to release of cancer cells in to blood or lymphatic stream in to the body as single cell or emboli . These emboli gets arrested in the draining sites like lymph nodes ,organs ,adhere to endothelial cells and capillary beds. Extravasation also involves same steps of invasion 8) Growth in the deposited organ of metastases depends upon the responses of paracrine and auto crine factors of the tumor,once metastases establishes it becomes a source for further metastases known as “ METASTASES OF METASTASES”.

The risk of relapse in carcinoma breast patients is more during the first 2 yrs after diagnosis and treatment, the time of events and survival of cells vary in circulation within minutes to years.

Genes associated with metastases in carcinoma breast are S100A4/MTA-1/ Osteopontin /bcl-2/maspin. Genes associated with suppressing of carcinoma breast are nm23/ KAI1 /KiSS 1/BRMS1. Metastases in breast cancer was described by Stephen Paget base on "seed and soil" hypothesis .

Role of surgery in metastatic breast cancer

At present carcinoma of breast has replaced carcinoma of cervix in Indian tumor registries. Survival of these patients has increased over the years. Over the years systemic therapy is the treatment of chronic and local therapy like Radiotherapy and Surgery.

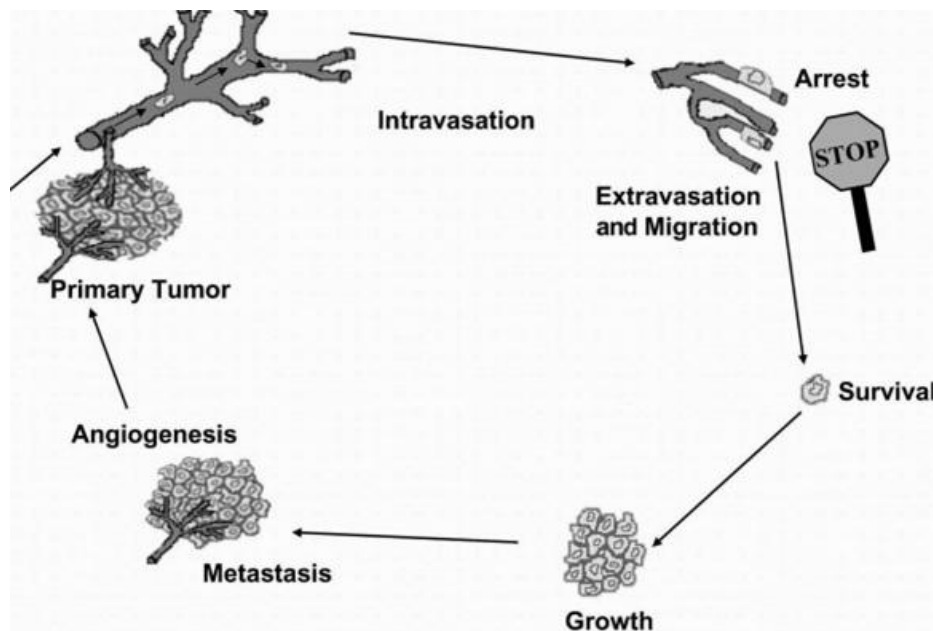
### **Mechanism of Metastases in breast cancer**

Halsted was the first person to state the therapy of metastases. According to him breast cancer is a localized disease in the breast and it

spreads to axillary nodes and to the sanctuary site. Hence he advocated extensive loco-regional treatment.

Bernard Fischer later defined that breast cancer was a systemic disease, which has a capacity to spread to other sites even before diagnosis. Later Spectrum theory emerged and stated that exact meaning of metastases to distant sites was unclear. Hence advised both systemic and local therapy.

#### STEPS IN METASTATIC PROCESS



### **Lang et al described three theories**

1. Parallel evolution, which says that circulating tumor cells present in the tumor is the cause for the metastases during tumorigenesis even before the development of the intact primary tumor.
2. Gene expression profile theory says that potential for metastases is an inherent property genetically present in breast cancer patients during early stages
3. Stem cell model says that metastatic potential of breast cancer or a specialized tumor initiating cancer cells.

Danna et al defined the concept of surgery in metastatic breast cancer by the theory of immune-suppression, which is reversible by the surgical removal of primary tumor. The first study in evaluating the treatment of metastatic breast cancer was by Khan et al in 2002, which was a retrospective study, which showed survival benefits.

### **Survival benefit?**

Question to be answered before initiating the treatment.

At present survival for visceral metastases is 6 months, nodal disease is 18 months, bone only disease is 3-4 years.

In Khan et al study which reviewed NCDB, 3 years survival was 24.9% for the whole group. Survival for total Mastectomy 31.9 months, partial mastectomy 26.9 months, no surgery 19.3 months .

There are several studies which showed survival benefit like Rapids et al, Gnerlich et al, Blanchard et al, McGuire et al , Babiere et al , Neuman et al, reported trends towards increased survival. But it was not statically significant.

### **Should lymph node dissection be done?**

The exact details are not reported not so far in most of the reviews. When the logic of improving the survival applies to removal of the primary, the same can be applied to ALND. Hence patient under going total Mastectomy can be given the benefit of ALND. NCDB conclude that ALND can be a contributing factor for survival with total mastectomy but it is an independent prognostic factor. Studies evaluating the benefit of ALND are Rapids et al, McGuire et al and Neuman et al. All these studies showed some survival benefit and advised ALND as a part of treatment approach.

Negative margin be attempted?



Even though negative margin is the fundamental concept of oncology, there is a lack of data towards the role of negative margin resection in metastatic breast cancer. The studies evaluating this are Rapids et al, McGuire et al and Khan et al. These studies supported the need for negative margins based on the review, which showed five-year survival of 27% for negative margin, 16 % for positive margin and 12 % for unknown margin. Hence it will be better to give negative margin.

### **When to operate?**

When the decision of loco-regional treatment is offered, then the timing of the surgery is to be decided. Based on the review of articles showed that surgery may be done after three months of initial diagnosis/chemotherapy improved progression free survival. The time gap between diagnosis/ chemotherapy makes the oncologist to study the behavior of the disease. Studies favoring this are Babiere et al, Neuman et al, and Rao et al.

### **Prospective Trials**

The MF 07-01 9(NCT00557986) is phase 3 RCT that compares metastatic breast cancers patients at presentation who receive loco regional treatment Vs no treatment and to assess the overall survival benefit, which was activated in 2007. Short interim remits in ASCO 2010 shows no evidence for surgery. Similar NCT 00193778 study from India familiar to show such benefit.

The current evidence is not enough to use surgery for primary MBC. However there is subset of patients who may be offered loco-regional treatment such as surgery to maximize survival.

## **CONCURRENT CHEMOIRRADIATION**

There is no enough dsatafavouring concurrent chemoirradiation in locally advanced breast cancer and metastatic breast cancer ,but there are studies favouring concurrent chemoirradiation in breast conservation surgery even though not practiced much.Studies favouring concurrent chemoirradiation are the following.

Study1: Argangelia et al did randomized study using concurrent Vs sequential CMF chemotherapy.

Sample size 206 pts, TD 50Gy/20# over 4 wks followed by 10-15 Gy electron boost following BCS. there was no difference in breast recurrence, metastases free, disease free, overall survival in the two treatment. all patients completed the total dose of RT and there was no difference in toxicity profile between the two arms, study showed that RT can be delayed for 7 months if margins were negative and considered concurrent CMF as a safe regimen and may be used in patients with high risk of local recurrence.

Study 2: Rousse et al study used FNC regimen consisting of Inj 5FU 500 mg/m<sup>2</sup> / Mitoxantrone 12mg/m<sup>2</sup>/ Cyclophosphamide 500mg/m<sup>2</sup> to sequential FEC regimen consisting of Inj 2FU 200mg/m<sup>2</sup>/ Epirubicin 60mg/m<sup>2</sup>/ Cyclophosphamide 500mg/m<sup>2</sup>.

Sample size 650 pts RT in node positive breast cancer pts. There was no difference in DFS or overall survival (3% Vs 7%) out of these 6 had LRR in concurrent arm and 18 had LRR in sequential arm.

Study3: Tolenado et al studied Arm –A sequential chemo +RT, Arm B concurrent chemo irradiation using FNC regimen consisting Inj 5FU/Mitoxantrone/Cyclophosphamide. Sample size 214 pts, local control was superior in concurrent arm but toxicity was more like subcutaneous fibrosis/ telangiectasia /skin pigmentation /breastatrophy.but there was no difference in Grade II skin reaction/breast pain/lymphedema

Study4: Calais et al similar to Rouse et al study .Toxicity was more, LC was good/LRR was low.

Study5: Bellon et al: was prospective single arm study which showed good local control in high risk group patients with le received concurrent CTRT 109 pts Vs 426 pts received sequential RT, local control and locoregional relapse was lesser in CTRT arm ,these studies did not use Adriamycin and taxanes.

Study7: Goyal et al studied using Bevacizumab in combinat concurrent CMF and lesser dose of RT.

Study: Retrospective study from Yaion with whole breast RT Vs RT alone there was no difference in grade III reactions/no fatigue of RT/RT fibrosis/ pneumonitis / lymphedema between the two arms.

## **HYPOFRACTIONATED WHOLE BREAST IRRADIATION**

It is growing trend at present which involves delivering higher dose per fraction with in a short period of time to a biologically equivalent dose .START Trial A -1-( pT1-3a pN0M0)-TD:50 Gy25#Vs 41.6Gy or 39Gy in 13# of 3.2Gy or 3.0Gy over 5weeks after surgery. Over all treatment time was kept constant in all three arms including SCL& Axilla. Primary end point was LRR .LRR at 5 yrs was 3.6% for 50 Gy/3.5% for 41.6Gy/5.2% for 39 Gy.START B Trial- (pT1-3a pNo-1 M0)-TD 50Gy25#/40Gy 15# of 2.67 Gy over 3 weeks .Here over all treatment time was not consistent.LRR at 5 yrs was 2.2 % for 40 Gy/3.3% for 50 Gy. Whelan et al study after BCS randomized to TD:50 Gy @25# vs 42.5 Gy@ 16#.LRR at 10 yrs was 6.7% for 50 Gy 25 #/6.2% for 42.5 Gy 16 #.

ASTRO 2011 concluded that hypofractionated whole breast irradiation is equivalent to conventional irradiation who meet the following criteria 1)50 yrs and above 2)pathologicT1-T2 N0 treated with lumpectomy 3)patient not receiving chemotherapy 4)minimum and maximum dose along central axis not <93% and not >107%.heart should be excluded from treatment fields during planning hypofractionated

RT.RTOG 1005 is phase III study on hypofractionated RT.Taking age/comorbidities/distance of RT facility in to consideration Hypofractionated RT may be offered to these patients. Accelerated Partial Breast Irradiation :

Even though whole breast irradiation is the standard of treatment for BCS patients APBI is an alternate approach which can shorten treatment time ,there by more easier for patient,easier delivery of radiation and chemotherapy ,also reduces the treatment cost.

The concept behind this approach is that much of recurrences occur at near the operated site.

This modality includes multicatheter interstitial implants which is placed around the operated site, Mammosite technology which uses single ballon catheter in were in a radiation source is afterloaded at the operated site ,external beam conformal partial breast irradiation and intraoperative single dose irradiation.

This modality has not yet under a randomized study to prove it is equivalent to whole breast irradiation . The current study under trail is NSABP-39/RTOG-0413 which allows one of three APBI techniques.

Multicatheter Interstitial Techniques: This modality includes tumors < 3 cm after lumpectomy, negative margins, 0-3 nodes positive, no ECE. Dose LDR APBI-45 Gy in 3.5 to 5 days or HDR APBI 34 Gy in 10 BD # within 5 days. No significant adverse effects were noted, No statistically significant ipsilateral breast recurrences, or LRR, OS, DFS. Studies evaluating APBI are Kuske et al , Vicini et al , Arthur et al , Wazer et al ,

Mammosite: More extensively used in America, this contains a catheter with a central balloon inflated at the lumpectomy site, the distance between balloon and skin is > 5mm or ideally >7 mm, treatment is delivered by HDR remote after loading system with 1 cm circumference around the tumor. Dose 3.4 Gy at 1 cm twice daily to a total dose of 34 Gy over 5 days. It was said that treatment benefit, cosmetic effect, toxicity at 5yrs using Mammosite was similar to other forms of APBI.

## **APBI (Accelerated Partial Breast Irradiation)**

External Beam Conformal Radiation.

At present over 70 percent of breast cancer patients being treated with 3D-CRT which is totally non invasive with homogenous dose delivery and distribution. Dose 38.5 Gy at 3.85 Gy/# delivered daily CTV included operated site + 1-1.5 cm clearance and 5 mm within the skin surface and chest – lung interface.

Intraoperative Accelerated Partial breast Irradiation: radiation dose is delivered using single intraoperative dose to the operative site at the time of surgery using intraoperative electrons or intra operative photons. Dose-20 Gy.

ASTRO 2009 consensus for APBI-patients > 60 yrs/node negative/invasive ductal tumors <2 cm/negative margins/ER+/no LVSI.



## **Bone metastasis**

Bone is the most common site of metastatic disease in the breast cancer and affects up to 70% of women with metastases. Metastasis occurs mostly in the axial skeleton.

Aim of treatment in bone metastasis is avoid skeletal related events. median survival after bone metastasis is 19-25 months. if a pathological fracture occurs it is reduced to 12 months.

Sometimes survival may prolonged with good risk factors like low grade tumours, bone disease at initial presentation, long disease free survival, hormone receptor positive . Bone-only disease has a better prognosis than disease associated with visceral involvement.

Treatment for metastatic breast cancer with bone metastasis is mainly hormone therapy therapies and bisphosphonates Radiotherapy plays a major role in the treatment of bone metastasis as a palliation. . It is of particular benefit for those patients with painful bone disease or

spinal cord compression and even in the face of a large burden of metastatic disease due to the high response rate and low toxicity.

### **EFFECTS OF RT ON BONE:**

The majority of bone destruction is mediated by osteoclasts, which are in turn influenced by humoral factors released by the tumor. Malignant stimulation of the RANK signaling pathway increases the osteoplastic activity. New bone formation is predominantly reactive, but may be exuberant, generating new bone that often lacks the strength of normal lamellar bone.

Pain may be either nociceptive (mediated by prostaglandins, substance P, and other cytokines) or neuropathic (as a result of bone destruction and increased resorption, peri-osteal irritation and nerve entrapment). The mechanism by which radiotherapy improves pain is not clearly understood.

### **Progression**

Either an increase in worst pain score of 2 or more at the treated site without reduction in analgesic use or an increase of 25% or more in

daily oral morphine. Equivalent compared with baseline without a reduction in baseline worst pain score.

### **Fraction in the treatment of localized bone metastases**

The largest single randomized study – the Dutch bone metastasis study (DBMS) (13) – randomized only 29% of eligible patients. All of the randomized studies included multiple different tumor types, but in all cases breast and/or prostate cancer formed the predominant patient groups. In the DBMS, 49.7% of the 1157 patients had breast cancer.

A single fraction of 8Gy delivered for palliation achieves a 60% response rate by intention-to-treat analysis. Approximately one-third of patients treated have a complete pain response. Overall, mean time to response is 3 weeks and mean duration of remission is 18 weeks. Single fraction are clearly more convenient for the patient and increase treatment capacity for the radiotherapy center. While single fractions are commonly employed in the United Kingdom and Canada, fractionated regimens such as 20Gy in 5 fractions or 30Gy in 10 fractions are the norm in the rest of the world.

## **Re-treatment of bone deposits**

Re treatment after a single fraction is recorded for 21.5% of patients as compared with 7.4% of those receiving multiple fraction. Single-fraction treatment has also been tested against multiple fractions in the treatment of neuropathic bone pain, where it has been argued that multiple fractions are required to required to reduce tumour mass and relive pressure on nerves .

### **Axial metastasis**

Presentation in the descending order in carcinoma breast

1. Vertebra primarily thorocolumbar
2. Pelvis
3. Ribs
4. Femur
5. Humerus
6. Other sites eg.scapula,tibia,skull

## **Spinal metastasis**

30-70% of patients with carcinoma breast has spinal metastasis at the time of death

Pain in spinal metastasis is due to release of local chemical mediators substance P, bradykinin and histamine and due to enlarging tumour mass, bone defect leading to pathological fracture /deformity kyphosis /scoliosis or both, nerve root compression due to tumour mass, compression of spinal cord due to tumour mass because of tissue reaction or fractured fragments

## **MANAGEMENT OF SPINAL METASTASIS**

Class I –no nerve involvement –chemotherapy or local RT

Class II –involvement of bone no collapse – chemotherapy or local RT

Class III – neurological involvement –without body involvement –local  
RT/steroids

Class VI – vertebral collapse with instability without nerve involvement  
– surgery

Class V – vertebral collapse with nerve involvement – surgery

Goals of spinal surgery should include neural decompression, spinal stability, correction of spinal deformity

However with the advent of minimally invasive spinal surgery it is concentrating on three main areas , biopsy , replacing bone loss by vertebroplasty and kyphoplasty , reconstruction and stabilization through endoscopic procedures

#### MANAGEMENT OF ACETABULAR METASTASIS

Class I –lateral cortex - superior medial walls intact – cemented THR

Class II – deficient medial wall – protrusio cup cemented THR

Class III – deficient lateral and superior wall – protrusion cup with fixation with cemented THR

Class IV – solitary metastasis resection of lesion – girdle stone saddle prosthesis of custom made prosthesis

Mirel's scoring system for appendicular metastasis

Location –peritrochantric (3) – lower extremity (2) – upper extremity(1)

Lesion type – lytic (3) -mixed: lytic & blastic (2)- blastic (1)

Amount of cortical loss  $\rightarrow$   $\frac{2}{3}$  (3) –  $\frac{1}{3}$  to  $\frac{2}{3}$  (2) -  $<\frac{1}{3}$  (1)

Pain - functional (3) – functional, moderate (2) – moderate (1)

A score of 8 and above is indicative of surgery 30 -50 % of loss in bone mineral density has to occur to be picked up on a plain X-ray film  $>50\%$  loss in thickness of cortical bone in plain X- ray signifies impending fracture and osteolytic lesion  $>2.5\text{cm}$  is considered significant

## **CHARACTERISTICS OF METASTATIC TNBC**

TNBCs have a poor prognosis in the adjuvant setting, characterised in particular by early recurrence compared to other subtypes of breast cancer. This occurs despite a high sensitivity to (neo) adjuvant chemotherapy. Although cancers that have a pathologic complete response (pathCR) to neoadjuvant chemotherapy have a good prognosis, those cancers that do not achieve a path CR have a marked poor prognosis with frequent and early relapse. Disease free survival at 4 years was 87% for those who had a path CR compared to 69% in those who did not.

A vast majority relapses from TNBC occur in the first 5 years following prognosis the reasons for poor prognosis in the metastatic setting are multi factorial. This reflects the lack of targeted therapies for TNBEC and the highly proliferative nature of TNBC this reflects the pattern of metastasis seen in TNBCs characterised by less frequent bone and liver metastasis and more frequent lung and brain metastasis. Current evidence suggests that triple negative basal like and non basal like breast cancers have similar pattern of metastasis

Molecular subtype is also predictive for risk of loco regional recurrence after these breast conserving surgery and mastectomy with contemporary trastuzumab containing adjuvant systemic therapy the outcome of the HER2 enriched group is now likely to have improved ,leaving BLBC as the cancer subtype with highest risk of local relapse.



## **LEPTOMENINGEAL METASTASES:**

It is commonly seen with lobular histology of carcinoma breast ,it arises mostly from the pia and arachnoid space or subarachnoid space ,spread is due through blood ,direct extension through venous plexus along nerves or perineural invasion .Once it reaches the meninges it spreads through CSF. Symptoms will be due to raised ICT ,local inflammatory responses like severe headache and vomiting ,focal neurological deficits,seizures.Investigation of choice will be Gadolinium enhanced MRI, prognosis is poor ,survival will be 5-7 months.

Radiotherapy to craniospinal axis is difficult due to bone marrow toxicity. Intrathecal chemotherapy and systemic chemotherapy is advised in these conditions.

## **INTRA MEDULLARY METASTASES:**

One of the rare presentation in breast cancer 0.1-6%, overall survival 13 months .commonly involves cervical spine. Clinical signs depends upon the level of involvement. Investigation of choice is MRI

(iso intense and nodular on T1 images and pencil shaped hyper intense on T2 images .Treatment involves steroids and radiotherapy.In patients with stable disease and without leptomeningeal spread surgery can be attempted.

### **EPIDURAL METASTASES:**

The most vascular portion which is the posterior part vertebral body is the site of metastases, commonly involves thoracic vertebra(50-60%),lumbar (30-35%),cervical(10-115%)in proportion to the volume of bone marrow . Back pain is the most common symptom ,myelopathy due to spinal cord compression , sensory disturbances. Investigation of choice will be MRI ,plain X-ray may be useful to see the stability of spine .

### **Goal of treatment**

1. preserve neurological function
2. relieve pain
3. preserve stability of spine.

Conservative treatment includes inj dexamethasone, radiotherapy with one level above and one level below. Surgery involves laminectomy and spinal stabilization followed by post op RT after 3 weeks. Surgery may involve anterior or posterior decompression .Recent advances in treatment involves procedures like vertebroplasty or kyphoplasty .

“To cure sometimes To relieve sometimes To comfort always .”

## **TREATMENT**

Carcinoma Breast has been divided into Early stage, Locally advanced and metastatic breast cancer. Treatment options vary according to the stage of the disease. The surgical management of breast cancer improved a lot for the past 30 years. Inially according to Halsteadian principles aggressive surgical management was done by Classical radical mastectomy.

Another hypothesis suggested that the extent of surgical resection alone not sidnificantly affect patients outcome and this supported bt trials also. As a result administration of poatoperative systemic

chemotherapy, hormonal therapy or both become standard practice for the majority of the patients. It reduces the rate of recurrence and metastasis ,so increases the overall survival. So surgery may be modified radical mastectomy or breast conservative surgery.

Neoadjuvant chemotherapy plays a major role in locally advanced breast cancer to make the inoperable tumors to operable one. Even in operable tumorsneoadjuvant therapy is used before breast concervative surgery.

## **SURGERY:**

The surgical management of patients is involves both the primary tumor and regional lymphatics. The primary tumor may be managed by modified radical mastectomy or Breast conservative surgery .Axilla is treated by either axillary dissection or sentinallymphnode biopsy.

## **CHEMOTHERAPY**

### **SCIENTIFIC RATIONALE for primary systemic chemotherapy**

The role of is primary systemic chemotherapy or neoadjuvant chemotherapy was justified by several hypothesis.it indicated that non

courative reduction of tumor cell burden increased the proliferative cells. After surgery of the primary tumour there is an increase in the proliferation of remaining tumour cells in the metastatic sites. This change occurs even after primary tumour irradiation. Removal of a primary tumor exerts its effect over the metastatic sites and causes stimulation of growth following surgical removal or reduction was due to soluble growth factor..

The neoadjuvant chemotherapy helps to decrease the micrometastases and prevent cancer growth cyclophosphamide, tamoxifen and radiotherapy prior to surgery prevent kinetic alterations suppresses tumor growth which in turn may increase the survival.

The Goldie – Coldman hypothesis

As tumor cell population increases, an ever expanding number of drug resistant phenotypic variants arise time to spontaneous somatic mutations that become more difficult to eradicate. The resistant cells can be minimized by initiating combination of non cross resistant drugs when the tumor cells are less in number. When the tumor grows not only the number of resistant cases increases and so is the proportion of resistant cells in the total cell population. Resistant phenotypes

multiply not only as a results of their own intrinsic growth rates and also due to the addition of new mutation.

Increased proliferation of cells following surgery causes increase in the number of resistant phenotypes in the metastasis. Neoadjuvant therapy not only stop cell proliferation but also eliminate cells that would have been made more sensitive by their kinetic alteration following surgery.

### **Scientific rationale for adjuvant chemotherapy**

Skipper and schabelconcept

They proposed that growth fraction and doubling times of tumors differs in from those in micro metastasis. So later they may well respond to adjuvant chemotherapy. After the primary surgery with decrease in tumour burden may alter the growth charecteristics and increase the chemosensitivity of the adjuvant treatment. It justifies the adjuvant chemotherapy.

### **Advantages of neoadjuvant chemotherapy**

1. Chemotherapy response can be assessed in vivo
2. Downstaging of the primary tumour and nodes.
3. Feasibility of surgery is enhanced due to reduction in tumour growth
4. Response to the chemotherapy act as a prognostic factor for long term survival.

### **Disadvantages of neoadjuvant chemotherapy**

1. It delays the effective primary therapy
2. Imprecise clinical and radiological staging
3. Loss of prognostic significance of axillary nodal statusUnknown relevance of surgical margin
4. Large no of drug resistant cells may present
5. Response to the primary tumour may not correlate with the response to the micrometastasis

Anthracycline and Taxane based chemotherapy regimens are currently the most effective agents for women with locally advanced and operable breast cancer. The most recent Eastern Breast Cancer Trialists Group (EBCTCG) results published in 2005 concluded that treatment with approximately 6 months of anthracycline-based chemotherapy with a regimen such as 5-fluorouracil, Adriamycin, and Cyclophosphamide (FAC) reduces the annual breast cancer death rate by about 38% for women younger than 50 years of age and by about 20% for those of age 50 to 69.



This meta-analysis also confirmed a moderate but highly significant advantage for anthracycline-based regimens (those including Adriamycin or Epirubicin) to regimens consisting of Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in trials involving more than 14,000 patients. The Cancer and Leukaemia Group (CALGB) 9344 study randomized 3121 women who had node-positive breast cancer to four cycles of AC or four cycles of AC followed by four cycles of Paclitaxel (AC-T) with dose-escalated doxorubicin. The addition of Paclitaxel was associated with significant 5-year DFS (70% versus 65%) and OS (80% versus 77%) benefits.

- Paclitaxel 200mg/m<sup>2</sup> IV over 3 hrs on day 1, repeat cycle every 21 days.
- Docetaxel 75 mg/m<sup>2</sup> IV on day 1, repeat cycle every 21 days.
- Paclitaxel + bevacizumab - Paclitaxel: 90 mg/m<sup>2</sup> IV on days 1, 8, 15.
- Bevacizumab; (Monoclonal antibody) anti vegf –antibody 10 mg/m<sup>2</sup> on days 1 and 15, repeat Cycle every 21 days.

## **CHEMOTHERAPY RESPONSE ASSESSMENT**

Tumour response assessment usually occurs 8-12 weeks after the starting of chemotherapy and comprises a summary of radiological and clinical responses, symptomatic benefit (including any improvement in performance status) balanced against toxicities of treatment. Radiological response (determined by response evaluation criteria in Solid Tumours (RECIST) criteria, is an improvement guide to the clinician in deciding whether to continue or change therapies.

While objective tumour responses (i.e., tumour shrinkage by more than 30%; Table @) set the standard used in clinical trials to judge the efficacy of chemotherapy, stabilisation of disease by RECIST criteria with a symptomatic benefit is an equally important endpoint. In patients with non-measurable disease, (e.g., bone-only disease) treated with chemotherapy, serial tumour markers together with symptomatic benefit are important indications of response to treatment.

**Miller-Payne histological criteria for grading response to solid tumours to chemotherapy in breast cancer.**

Grade	Description
1	No change
2	A minor loss up to 30% loss
3	Between 30% and 90% reduction in tumour cells
4	A marked disappearance of tumour cells more than 90% loss of tumour cells
5	No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastoticstroma remains often containing macrophages. However, ductal carcinoma in situ (DCIS) may be present

**RADIOTHERAPY**

The worldwide trend to be less radical treatment in the management of Carcinoma Breast has led to increasing role of radiotherapy in this disease. The first major use of radiotherapy in breast cancer was adjuvant to radical mastectomy. As the risk of local recurrence after mastectomy was 10 to 15% it was hoped that prophylactic radiotherapy would decrease this. Fletcher has also stressed

the judicious use of postoperative radiotherapy since the probability of control of gross local or regional recurrence from breast cancer is less than 60%. Post operative radiotherapy helps to decrease chances of local recurrence and increase local control & hence increase survival.

The technique of breast irradiation has evolved from use of conventional two dimensional planning with and without using wedges to 3 D conformal radiotherapy and intensity modulated radiotherapy (IMRT). Standard opposed tangential fields with appropriate use of wedges to optimize dose homogeneity remain the most commonly employed method for delivery of whole breast irradiation. These approaches include multicatheter interstitial implants placed around the excision cavity, single balloon catheter that can be afterloaded with a central radiation source (MammoSite) which is placed into the excision cavity, external beam conformal partial breast irradiation, and intraoperative single-dose irradiation.

Even after mastectomy and systemic therapy occult disease may remain in the chest wall and or regional lymph nodes. The residual disease may serve not only as a source of potentially morbid loco-

regional recurrence but also an important reservoir from which distant metastases may be seeded after the initial elimination of distant disease by systemic therapies. Therefore postmastectomy radiation therapy (PMRT) is an essential part of the treatment. Postop RT decreases risk of loco regional recurrence by treating residual microscopic disease that has spread beyond margins of surgical resection. The term local recurrence means the evidence of disease appearing in scar site or skin belonging to breast anatomical area or nodal drainage areas after adequate primary management.

Loco-regional failure can occur in the following sites

1. Ipsilateral chest wall/ Mastectomy Scar
2. Axillary Lymph nodes/Soft tissues
3. Supra/Infraclavicular Lymph nodes
4. Internal mammary Lymph nodes

### **Types**

1. Skin 2. Scar 3. Nodal 4. Combined.

Local skin recurrence may be nodular or inflammatory. Nodular may be solitary or multiple occurring most frequently in skin or

subcutaneous tissues in and around mastectomy scar. Small nodules are usually asymptomatic while larger ones can cause pain, itching or ulceration. In advanced situation confluent nodules may encircle chest to form cancer encuirasse.

The inflammatory type also called as erypseloid is less common. The lesion appears as diffuse reddening of skin associated with slight induration and increase in local temperature. Patients with this type of recurrence have poor prognosis and usually die of widespread metastatic disease within a short span of time. The scar recurrence is usually in the form of nodules or ulcers. Lymph node recurrence takes the form of nodules growing and getting fixed and ulcerating producing lymphedema of arm and painful limitation of arm movements.

### **Principles Of Concurrent chemoradiation:**

Concurrent chemoradiation has produced important improvements in treatment outcome. Randomized clinic trials show improved local control and survival through the use of concurrent chemotherapy and radiation therapy for patients with high-grade gliomas and locally advanced cancers of the head and neck, lung, esophagus, stomach, rectum, and anus.

The first mechanism is radiosensitization.. The underlying concept is that the observed effect of using chemotherapy and radiation concurrently is greater than simply adding the two together synergy cannot be determined simply by normalizing the radiation cell-survival curve for drug-induced cytotoxicity

A second proposed reason to combine radiation and chemotherapy is to realize the benefit of improved local control radiation along with the systematic effect of chemotherapy; a concept called spatial additivity.

Although concurrent chemotherapy has improved survival and organ conservation, further advances are limited by the toxicity of treatment. For example, in the curative treatment of locally advanced head and neck cancer with chemoradiation. It is now standard to place a gastrostomy tube prophylactically that they are unable to maintain adequate nutrition orally. The toxicity of treatment results from the relative lack of specificity of both radiation and chemotherapy for cancer cells as opposed to rapidly dividing normal cells.

## MECHANISMS OF LOCAL RECURRENCE

1. Extra mechanism is unknown Proposed theories include
2. Seedling from peripheral extensions of tumour
3. Implantation from vessels that ooze blood or lymph containing tumour emboli.
4. Retrograde movement of tumour cells to edge of the wound
5. Immunological factors.

Chest wall is the most common site of recurrent disease, accounting for two-thirds to three-quarters of all local-regional recurrences.

## RISK CATEGORIES FOR LOCOREGIONAL RELAPSES AFTER MASTECTOMY AND AXILLARY CLEARANCE

RISK CATEGORY	LOW	INTERMEDIATE	HIGH
RISK	<10%	10-20%	>20%
TUMOUR STAGE	T1-T2	T1-T2	<b>T3-T4</b>



NO OF AXILLARY NODES	0	1-3	>3
GRADE	1-2	3	
VASCULAR INVASION	-	+	
HISTOLOGY	DUCTAL	LOBULAR	

### **RISK OF AXILLARY RECURRENCE**

1-3 +VE LN (10YR-LRF)	
2-5 LN dissected	7%
6-10 LN	5%
>11LN	1.5%
>4 +VE Ln (10yr-lrf)	
4-5ln DISSECTED	12%
6-10	8%
>11 LN	6%

Early breast cancer Trialists' collaborative group and 2002 Cochrane review have shown that postoperative radiotherapy decreases recurrence rates by two thirds. Post operative RT decreases recurrence rates in stage 1 by 5%, stage 2 by 10% and stage 3 by 10 to 15%.

## **REVIEW OF LITERATURE**

### **ROLE OF SURGERY**

#### **Prospective Trials**

The MF 07-01 9(NCT00557986) is phase 3 RCT that compares metastatic breast cancers patients at presentation who receive loco regional treatment Vs no treatment and to assess the overall survival benefit, which was activated in 2007. Short interim results in ASCO 2010 shows no evidence for surgery. Similar NCT 00193778 study from India failed to show such benefit.

The current evidence is not enough to use surgery for primary MBC. However there is subset of patients who may be offered loco-regional treatment such as surgery to maximize survival.

## **ROLE OF RADIOTHERAPY**

### **Review of literature**

.A study from the Centre René Huguenin (Paris, France), loco regional radiotherapy was significantly associated with increased survival on multivariable analysis. In this study they were rarely used surgery as a primary treatment in metastatic breast cancer. They used locoregional radiotherapy as a main modality. The conclusion in that trial was locoregional radiotherapy ,may be an alternate modality for surgery in metastatic breast cancer with less morbidity 11

Another study from the Institute Gustave-Rousse (Paris, France), 239 women with stage IV breast cancer received loco regional treatment, either with radiotherapy alone or surgery with or without radiotherapy. In this study there was no significant difference in overall survival was observed, again it showed that radiotherapy, without surgery, was an adequate loco regional treatment metastatic breast cancer of women.

### **Retrospective Studies**

A trial from Tata Memorial Hospital (Mumbai, India) was initiated in 2005.<sup>1</sup> In this trial, chemotherapy is given before any

locoregional treatment. Preliminary results reported that 72% of patients in the locoregional treatment arm are free of disease progression compared with 61% in the observation arm. On multivariable analysis, locoregional treatment is a significant factor for progression-free survival.

## **THEORETICAL ADVANTAGES OF LOCOREGIONAL TREATMENT OF THE PRIMARY DISEASE BY SURGERY**

1. **The removal of the intact primary tumor has been** hypothesized to potentially reduce hematogeneous seeding by micrometastatic populations since local disease may serve as a hub of tumor stem cells
2. Another theoretical advantage of loco regional treatment in the setting of stage IV disease can reduce levels of circulating tumor cells that improved disease response and survival, and longer time to progression are associated with a lower number of circulating tumor
3. .Some biologists contend that tumor dissemination can compromise the immune system. The primary tumor can produce immunosuppressive factors that may help cancer cells avoid eradication by the immune system. In this context, surgical resection can reduce tumor load and lessen harmful immuno-suppression.

- **A Theoretical Disadvantage of local therapy** is based on the hypothesis that the primary local tumor can secrete substances that inhibit new blood vessels that support tumor growth.
- Removal of the primary disease can induce an angiogenic surge and promote the progression of metastases.
- Some believe that trauma induced by surgical intervention and general anesthesia can generate cytokines that stimulate neoplastic proliferation and compromise the integrity of the immune system.

#### Advantages of radiotherapy

Radiotherapy is a scientific surgery

1. Non invasive
2. No risk of anaesthesia
3. No risk of comorbidities
4. Can be given in patients with disseminated disease.
5. Skin is the best dressing and protection of the tumor which is not disturbed .
6. Cost effective , no need of hospital admission

## **AIM OF THE STUDY**

Aim of this retrospective study is to evaluate the role of loco regional treatment such as local radiotherapy and surgery in the management of patient with metastatic breast cancer.

## **METHODS AND MATERIALS**

**Study design:** This study is a retrospective study to evaluate the role of loco regional treatment such as radiotherapy and surgery in Metastatic Breast Cancer.

### **Inclusion and exclusion criteria**

#### **Inclusion criteria**

In our retrospective study we reviewed female patients with metastatic breast cancer registered at cancer Institute were analyzed from the year 2003 to 2008.

### **Inclusion criteria for this study were the following**

#### **Study setting**

All medical records of female patients with metastatic breast cancer registered at cancer Institute from the year 2003 TO 2008 and



who fulfil the inclusion and exclusion criteria of the study were reviewed and included in this study

### **Duration of the study**

patients from the year 2003 to 2008

### **SAMPLE SIZE:**

195 patients (120 patients underwent loco regional treatment 75 no treatment)

### **TREATMENT PROTOCOL**

All patients were treated with chemotherapy with or without concurrent radiotherapy. After six months of initial treatment response was assessed and decision regarding surgery was taken. Radiotherapy was given concurrently with chemotherapy.

### **Whole Breast Irradiation**

Treatment volume

The areas treated generally include the whole breast with or without supraclavicular, axillary regions. The entire breast and chest wall are included in the irradiated volume. The upper margin of the

portals should be placed at the head of the clavicle to include the entire breast. The medial margin should be at or 1cm over the midline. The lateral posterior margin should be placed 2cm beyond all palpable breast tissue. Which is usually near the mid-axillary line. The inferior margin is drawn 2 to 3 cm below the inframammary fold. In patients treated with 6-MV or lower energy photons with side tangential fields.



The entire ipsilateral breast should be encompassed. Conventional field borders are used. BREAST is treated using two tangential fields, medial and lateral tangents. Superior border is kept at second intercostal space. Medical border is at midline or matched with internal mammary

field when used. Lateral border is kept at midaxillary line. Inferior border is at 2 cms below opposite inframammary fold.

## **SUPRACLAVICULAR FIELD**

Supraclavicular nodes are usually encompassed, with a single anterior oblique photon field angled slightly away from the spinal cord. The medial border is placed at the insertion of the clavicular head. The lateral border is placed to include approximately one-third of the humeral head. The inferior border is the inferior border of the clavicle or the superior border of the chest wall field. The superior border is set at the thyrocricoid groove. A humeral head block is added to block the humeral head and acromioclavicular joint<sup>54</sup>

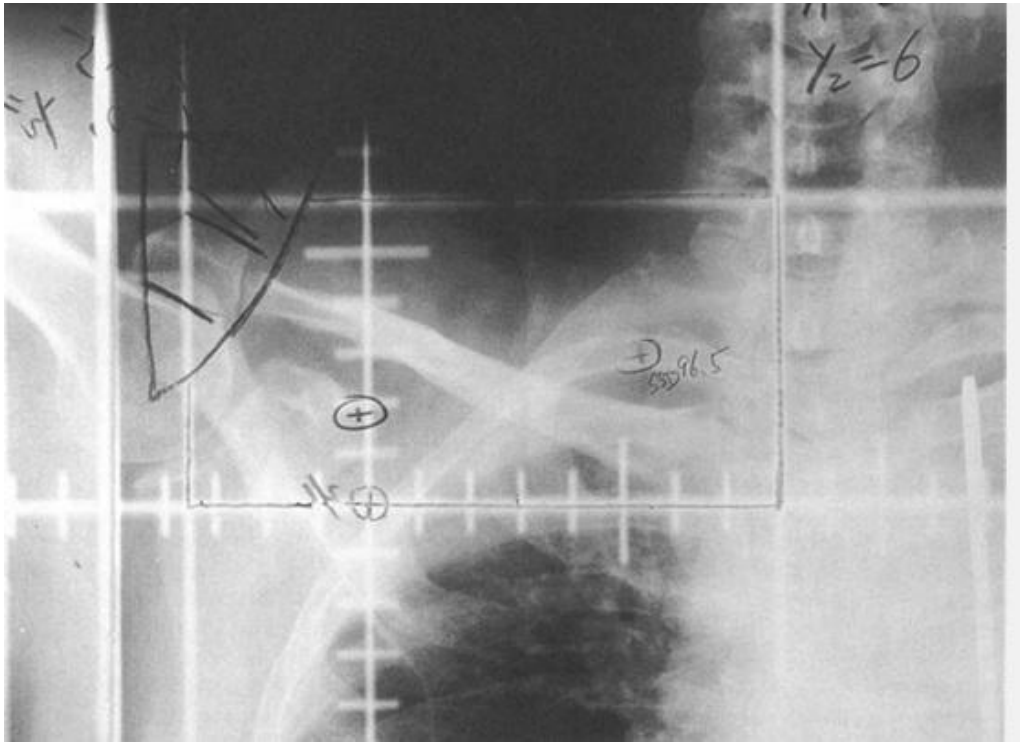
To avoid the problem of hot spot while matching supraclavicular and chest wall fields following methods are used. Angling the foot of the treatment couch away from the radiation source to direct the tangential fields inferiorly so that superior edge of these beams line up perfectly with inferior border of supraclavicular field. We can also use the three field single isocentre technique or Hanging block technique. Half beam block can also be used.

## **INTERNAL MAMMARY FIELD**

The internal mammary chain lies beside the sternum, generally in the first through the third intercostal space, although the depth may vary. Various methods of encompassing the internal mammary chain have been described, including extended tangent fields, partially wide tangent fields and matching electron and photon fields. But prophylactic internal mammary nodal irradiation is not recommended even in medial quadrant tumors.<sup>40</sup>

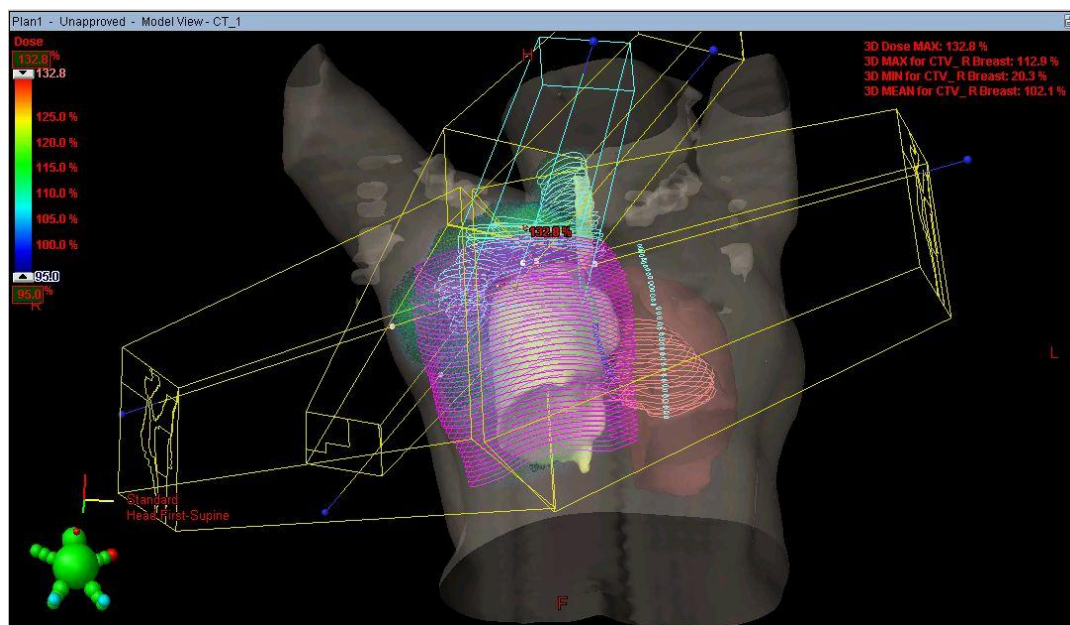
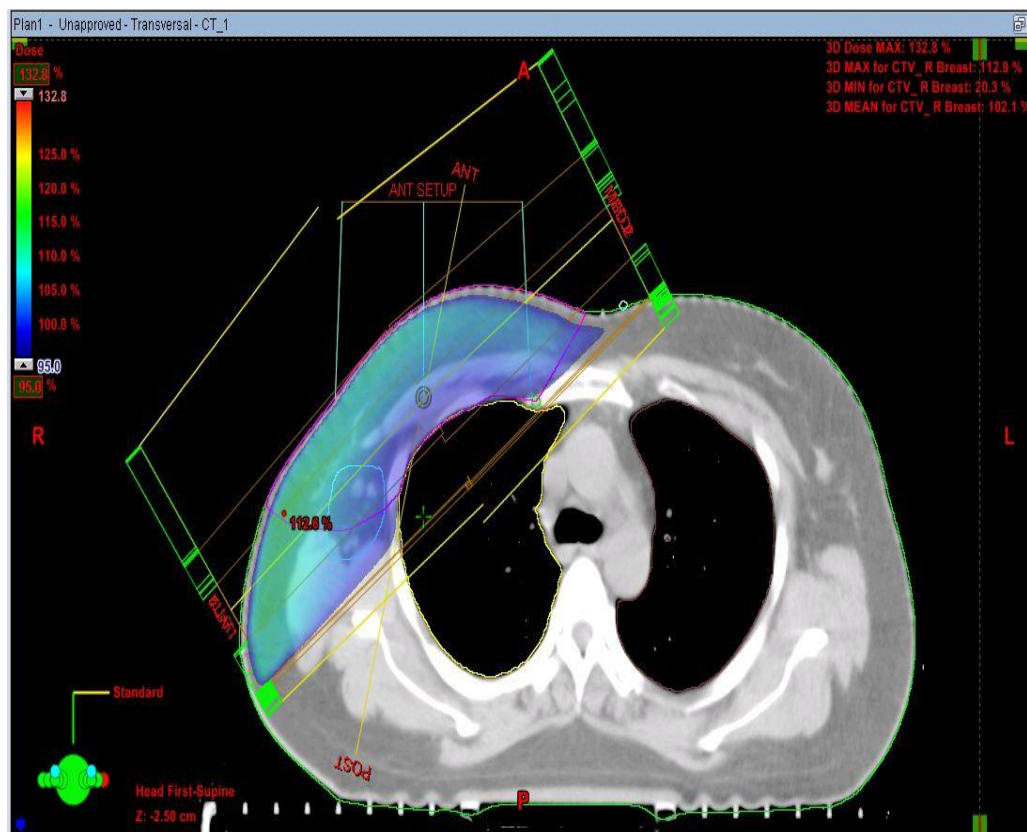
## **POSTERIOR AXILLARY BOOST**

The dose provided to the axillary nodes through the supraclavicular/axillary field can sometimes create suboptimal dose distributions to deeper lying level 3 axillary nodes. If coverage is suboptimal, the dose can be supplemented with a posterior axillary field. The field is set up opposed to the supraclavicular/axillary field. The medial border of this field is drawn to allow 1.5 to 2 cm of lung. If the inferior border is at the same level as the inferior border of the supraclavicular field, the lateral border just blocks falloff across the posterior axillary fold, the superior border splits the clavicle, and the superolateral border shields or splits the humeral head.<sup>54</sup>

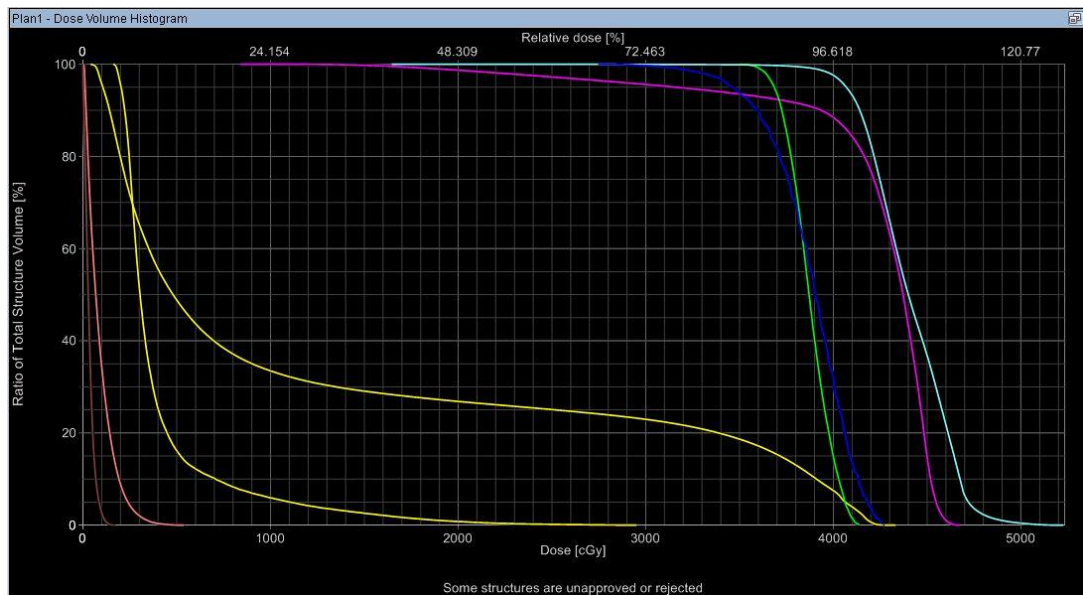


## DOSE

Most commonly employed dose schedule is 40-45Gy in 22- 25 fractions at conventional 180cGy daily for 5 weeks



## DOSE VOLUME HISTOGRAM



## FOLLOW UP

Subsequently patients were followed up monthly for the first year and once in threemonths for a period of five years from date of completion of radiotherapy after 5 years yearly follow-up was done

## ASSESSMENT TOOLS

Medical records were reviewed for the following factors.

1. age at diagnosis
2. laterality

3. histology of the tumor
4. clinical and pathologic size of the primary tumor
5. lymph node status
6. hormone receptor status
7. her 2 over expression
8. location and number of metastases mode
9. date of surgical treatment
- 10.t, margin status,
- 11.use of radiotherapy
- 12.systemic therapy
- 13.The time of death
- 14.the time of last review among alive patients
- 15.Patients with metastatic Breast cancer excluding brain metastasis at presentation were included.



## Patients baseline charecteristics

FACTOR	NO OF CASES	SURVIVAL PERCENTAGE			
		1 yr	3 yr	5 yr	10 yr
All cases	188	78	43	35	30
Pre Menopause	65	77	43	35	26
Post menopause	112	80	41	33	31
ER negative	55	75	40	36	34
ER positive	84	82	54	42	37
PR negative	66	76	41	33	32
PR positive	66	82	56	45	39
Her2 negative	31	94	68	61	58
Her2 positive	14	79	36	36	36
Metastasis 1	31	90	65	55	50
Metastasis 2	68	82	53	43	37
Metastasis 3	18	61	22	17	10
Metastasis 4	20	85	55	50	45
Metastasis 6	38	68	21	13	7
Metastasis 7	3	67	0	0	0
Metastasis 8	7	71	14	14	14

1vs 3=p value< 0.003

1vs 6=p value< 0.001

1vs 8=p value< 0.024

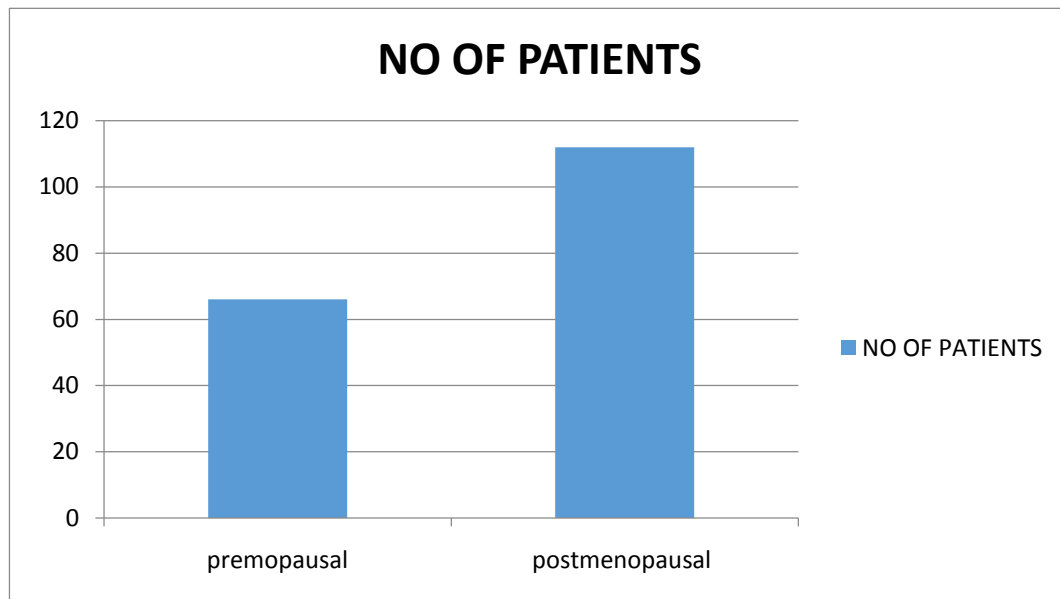
2vs 3 =p value<0.008

2vs 6=p value< 0.001

4vs 6=p value< 0.043

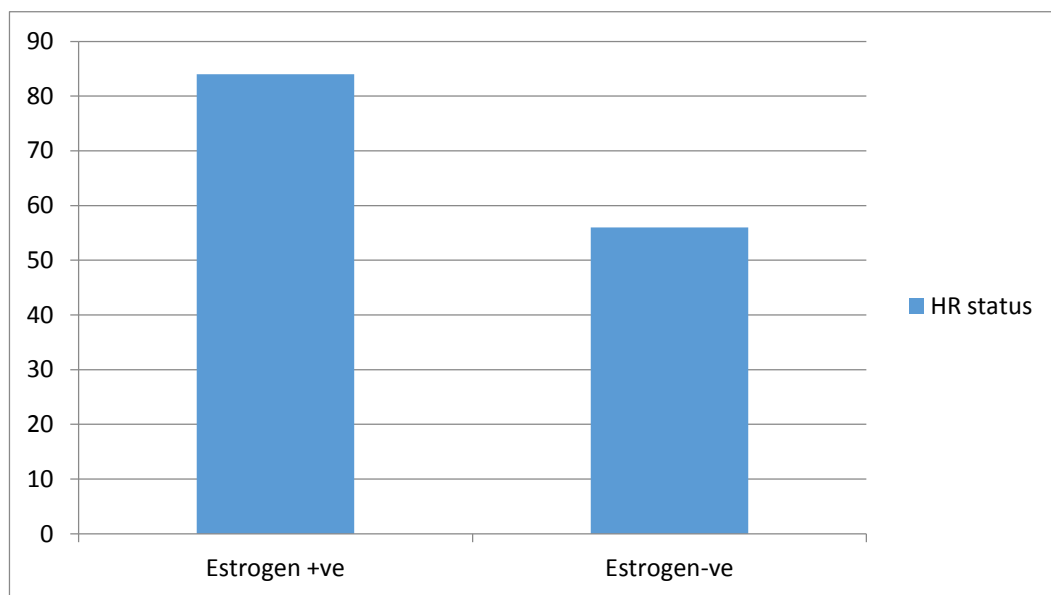


## MENOPAUSAL STATUS



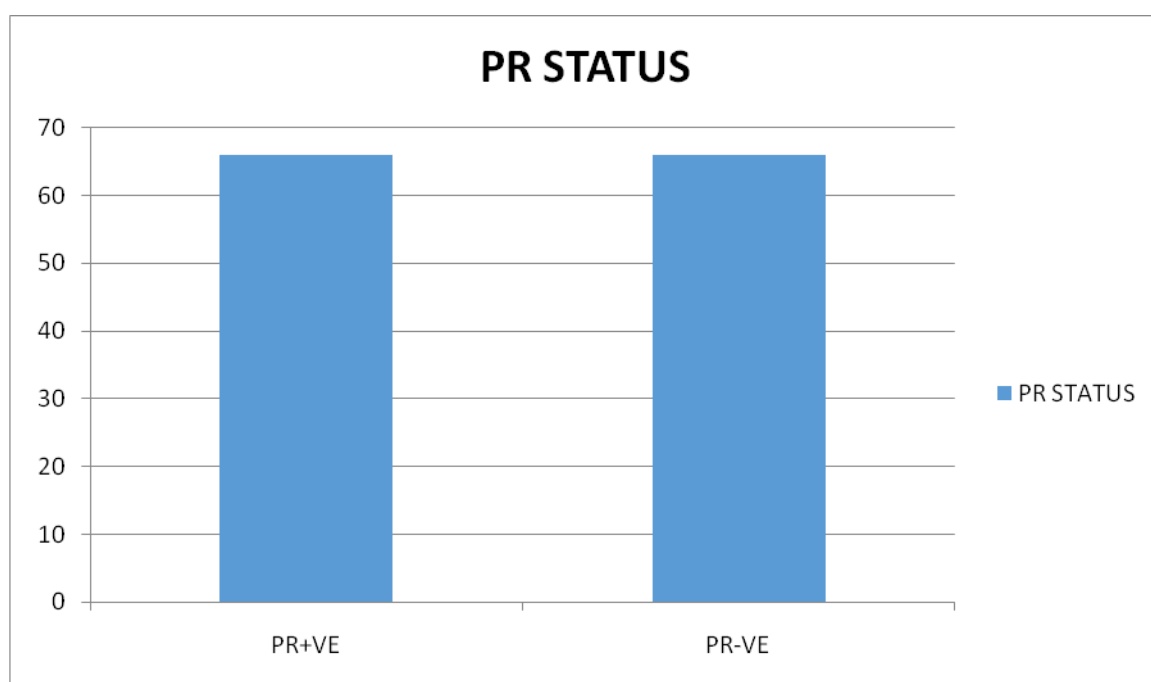
Most of the patients in this study were premenopausal.

## ESTROGEN RECEPTOR STATUS



Estrogen receptor status	No of patients
ER+ve	84
ER-ve	56
Status not known	55

## PROGESTERONE RECEPTOR STATUS



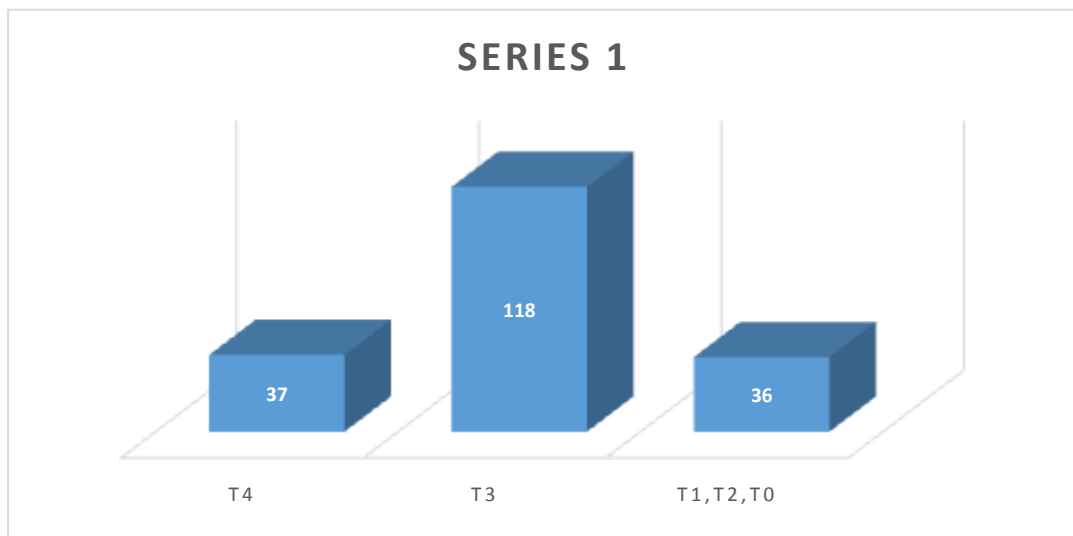
PR STATUS	NO OF PATIENTS
PR+VE	66
PR-VE	66

## Results

Tumour stage of the patients

Out of 195 patients 118 had T3 tumor size and 37 pts had T4 disease ,remaining 36 patients comes under T1,T2,T0

Tumor size	No of pts
T4	37
T3	118
T1,T2,T0	36



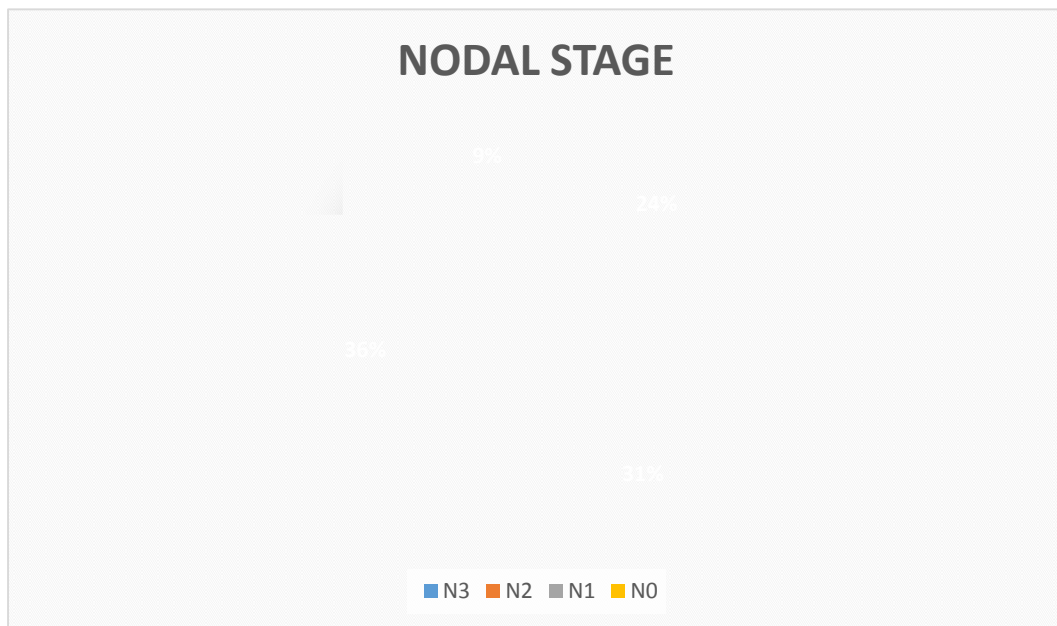
Most common tumour stage was T3

### **NODAL STAGE OF THE PATIENTS**

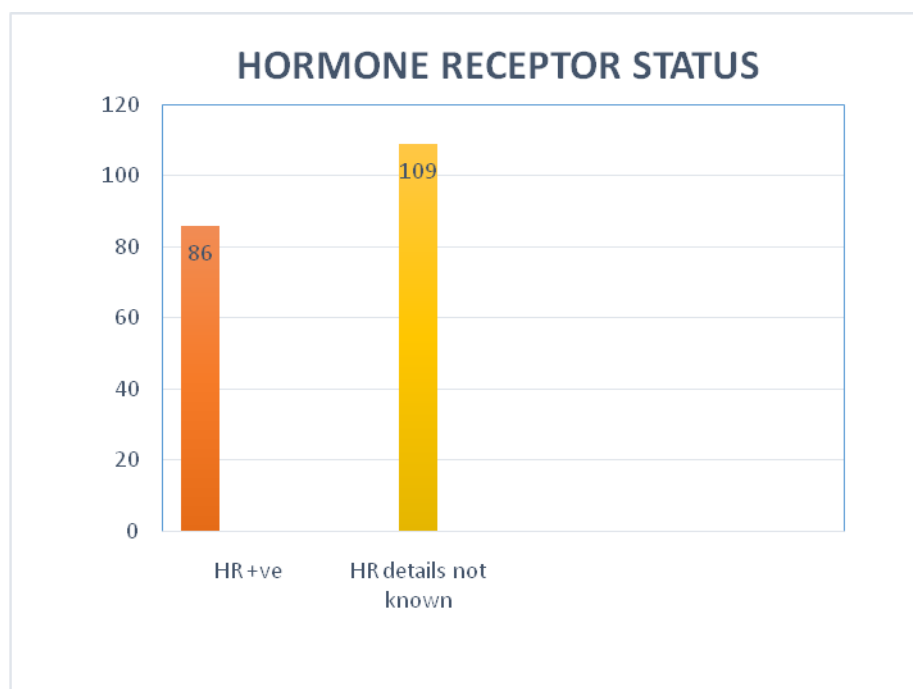
24% of the patients had N3 disease and 31 had N2 stage , 36% of them had N1 and 9%

Had N0 disease

NODAL STAGE	PERCENTAGE OF PATIENTS
N3	24
N2	31
N1	36
N0	9



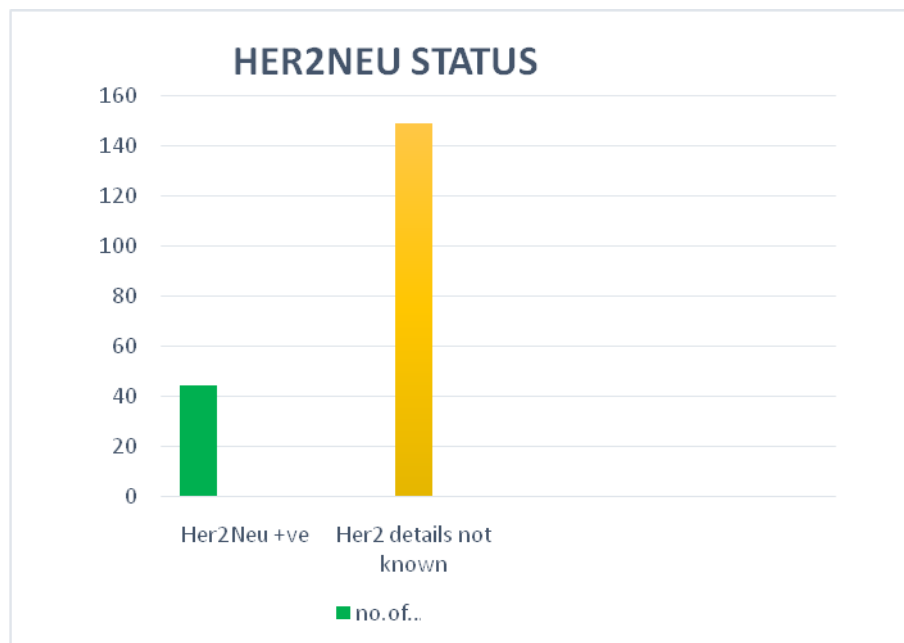
Most common nodal stage was N1



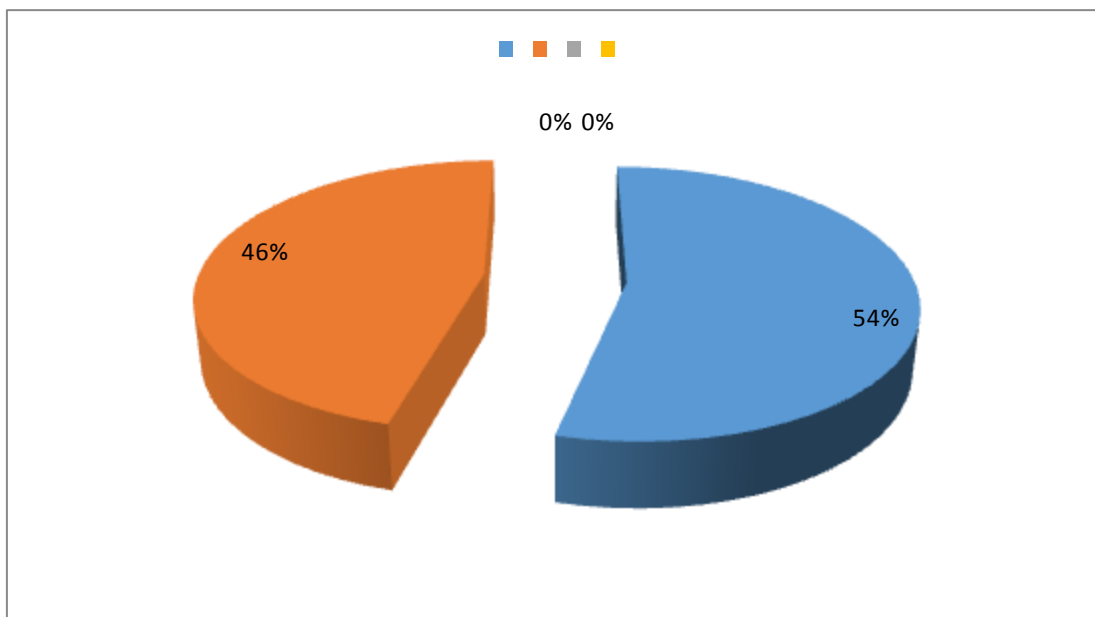
Out of 195 pts 86 pts are hormone receptor positive and in 109 pts the details of Receptor status not known.

<b>Receptor status</b>	<b>No</b>
<b>HR positive</b>	<b>86</b>
<b>HR not known</b>	<b>109</b>

Her2neu status of the patients



Graph:Percentage of patients with left and right sided tumours



#### Most common sides

In this study right sided tumours were found to be more common than left side tumours.

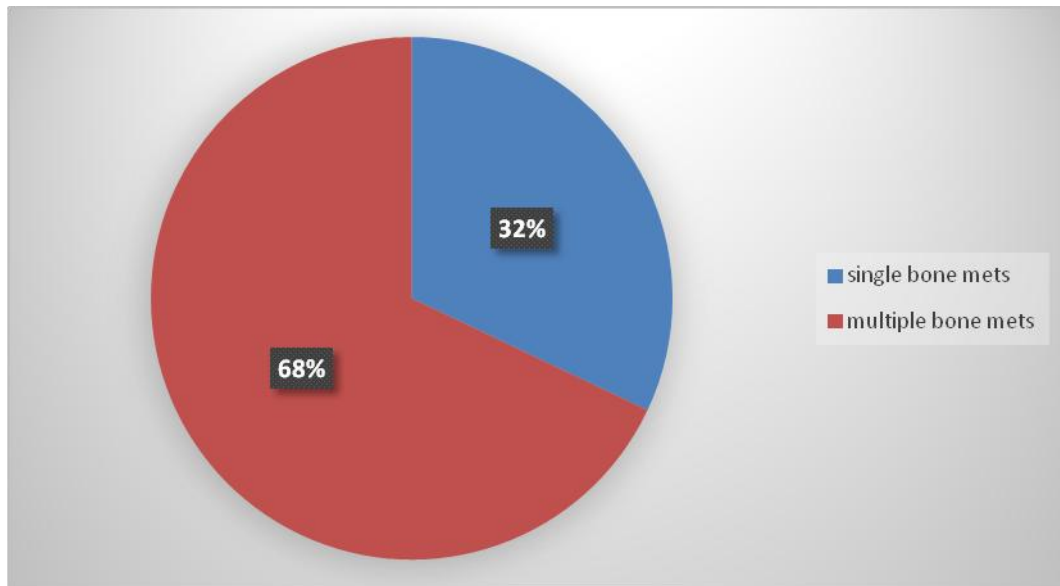
#### Incidence of bone metastasis

Out of 195 patients 33 patients (32%) had single bone metastasis and 70 patients (68%) had multiple bone metastasis

NO OF BONE METASTASIS	NO OF PATIENTS
SINGLE METS	33
MULTIPLE METS	70



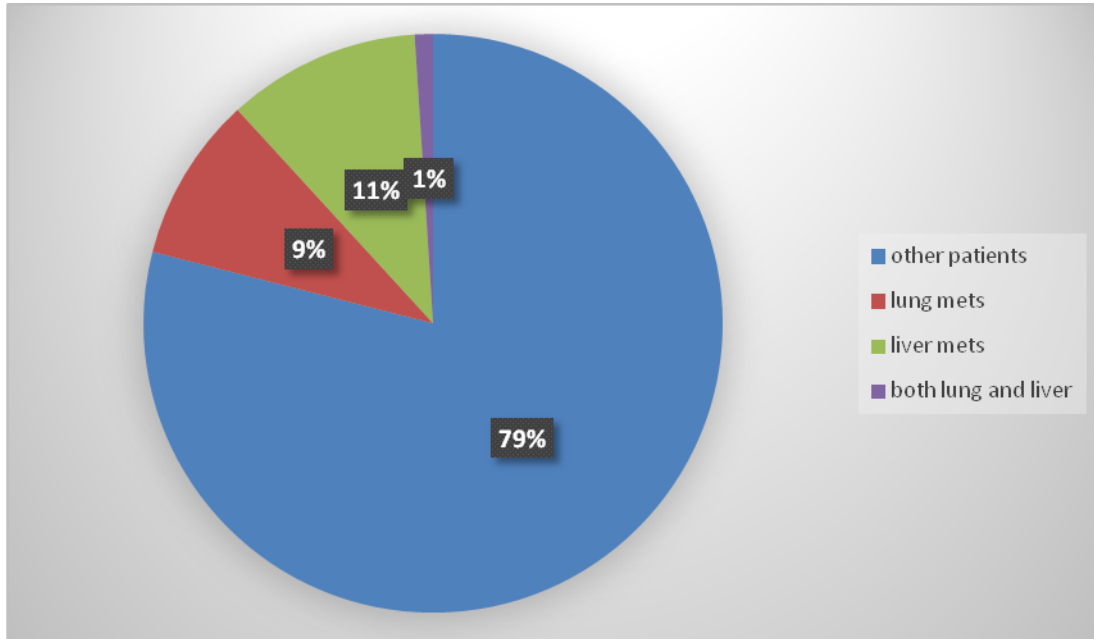
Graph : Percentage of pts with single and multiple bone metastasis



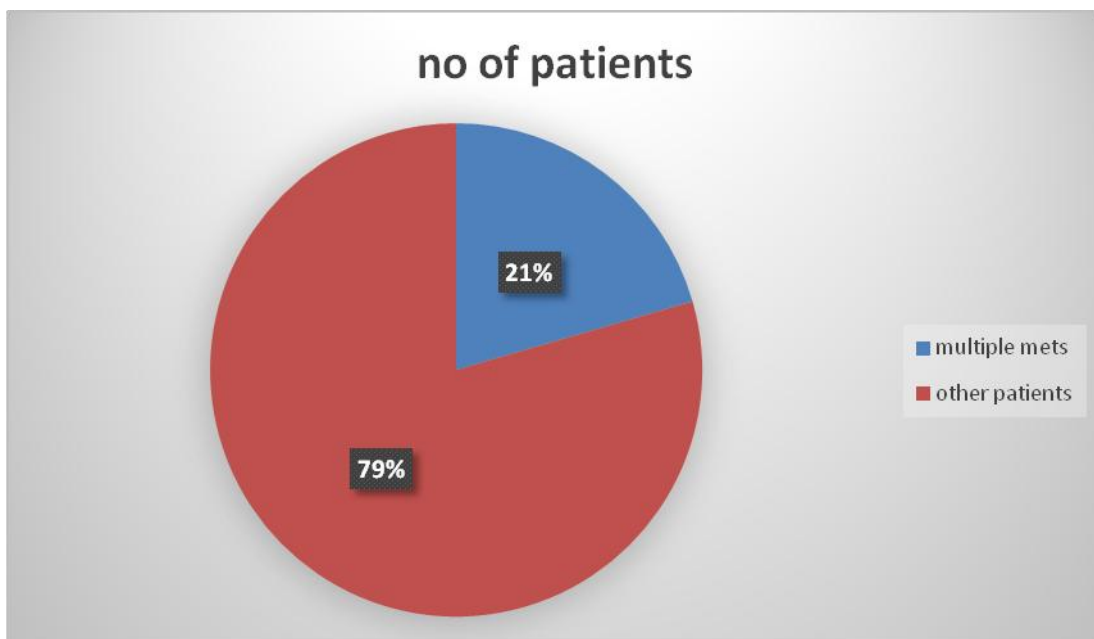
### LIVER AND LUNG METASTASIS

out of 195 total patients 18 patients (9%) had liver metastasis and 21 patients (11%) had lung metastasis ,two patients (1%) had both liver and lung metastasis.

Site of metastasis	No of patients
Liver	18
Lung	21
Both liver and lung	2



Patients with multiple metastasis



40 patients (21%) had multiple visceral and nonvisceral metastasis excluding brain which is not included in the study.

Total no of pts	195
Multiple mets	40

code for various treatment options

TRTCODE	Freq	Percent	Cum.	
2	74	37.9%	40.0%	RT+CT
3	2	1.0%	41.0%	CT+SX
5	37	19.0%	60.0%	CT+RT+SX
6	44	22.6%	82.6%	CT ONLY
7	3	1.5%	84.1%	RT ONLY
8	8	4.1%	88.2%	HT ONLY
9	12	6.2%	94.4%	CT+HT
10	5	2.6%	96.9%	RT+HT
11	6	3.1%	100.0%	CT+RT+HT
Total	195	100.0%		



1. code for various treatment options
2. chemorradiation (RT+CT)
3. chemotherapy +surgery (CT+SX)
4. Chemorradiation + surgery(CT+RT+SX)
5. Chemotherapy only (CTonly)

6. Radiotherapy only (RT only)
7. chemotherapy +hormone therapy (CT+HT only)
8. radiotherapy +hormone therapy (RT+HTonly)
9. chemotherapy+radiotherapy+hormone therapy (CT+RT+HT)

### **Various treatment OPTIONS**

Out of 195 patients with Metastatic Breast Cancer,

74 patients received chemoirradiation.

37 patients received chemoirradiation and then underwent surgery.

44 patients received chemotherapy alone.

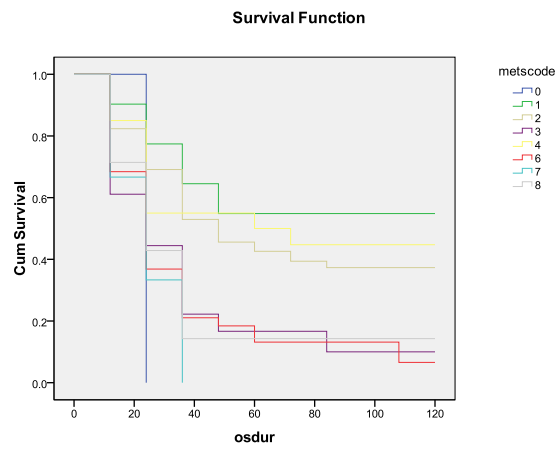
3 patients received radiotherapy alone.

2 patients received chemotherapy and surgery.

Total no of patients	195
chemoirradiation	74
CT +SX	37
CT	44
RT	3
SX	2

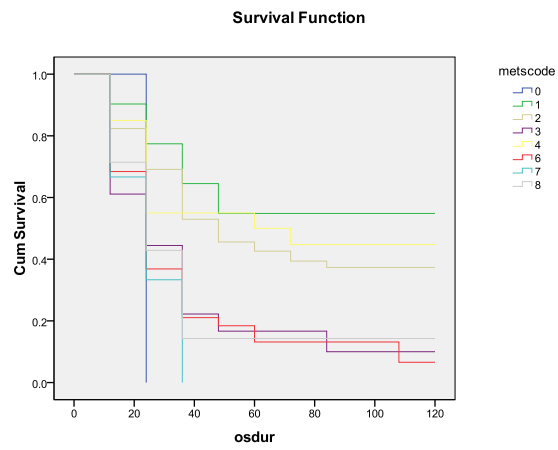
y

1. y



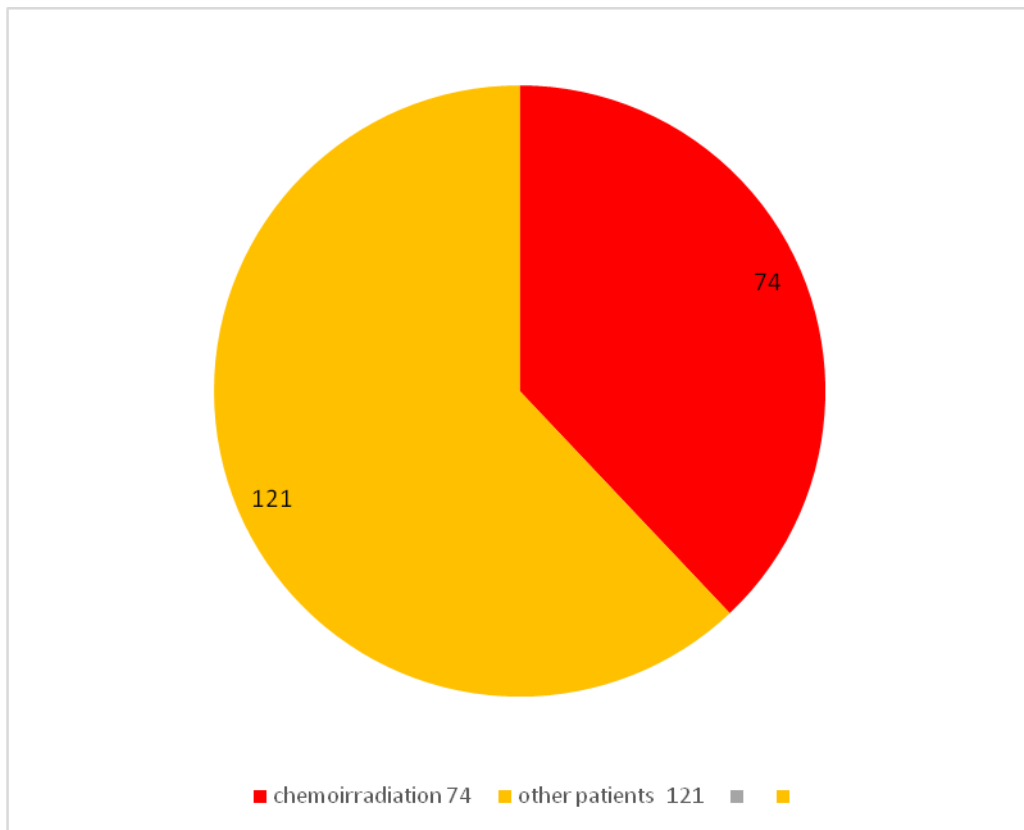
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## CHEMOIRRADIATION

Out of 195 patients 74 patients received chemoirradiation .

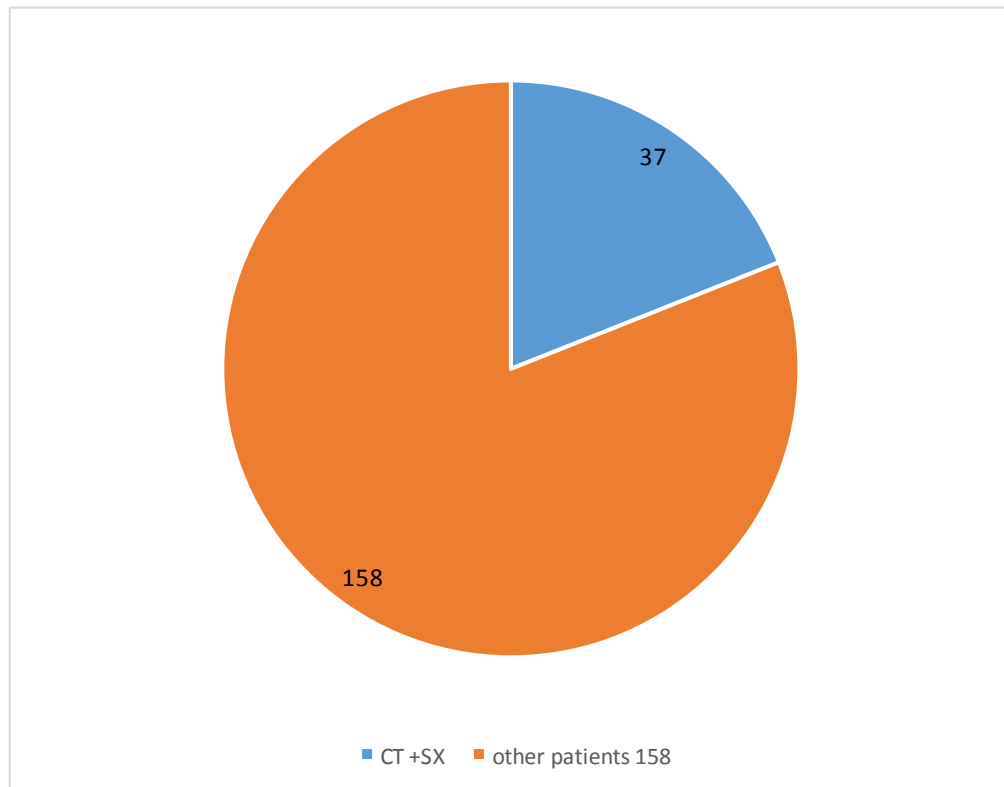


## RESULTS

In patients receiving CT+RT survival at the end of 1 yr was (89%) 3 yr (58%) 5 yr (46%) 10 yr,(42%).

## CHEMORADIATION AND SURGERY

Out of 195 patients 37 patients received chemoirradiation and then underwent surgery.

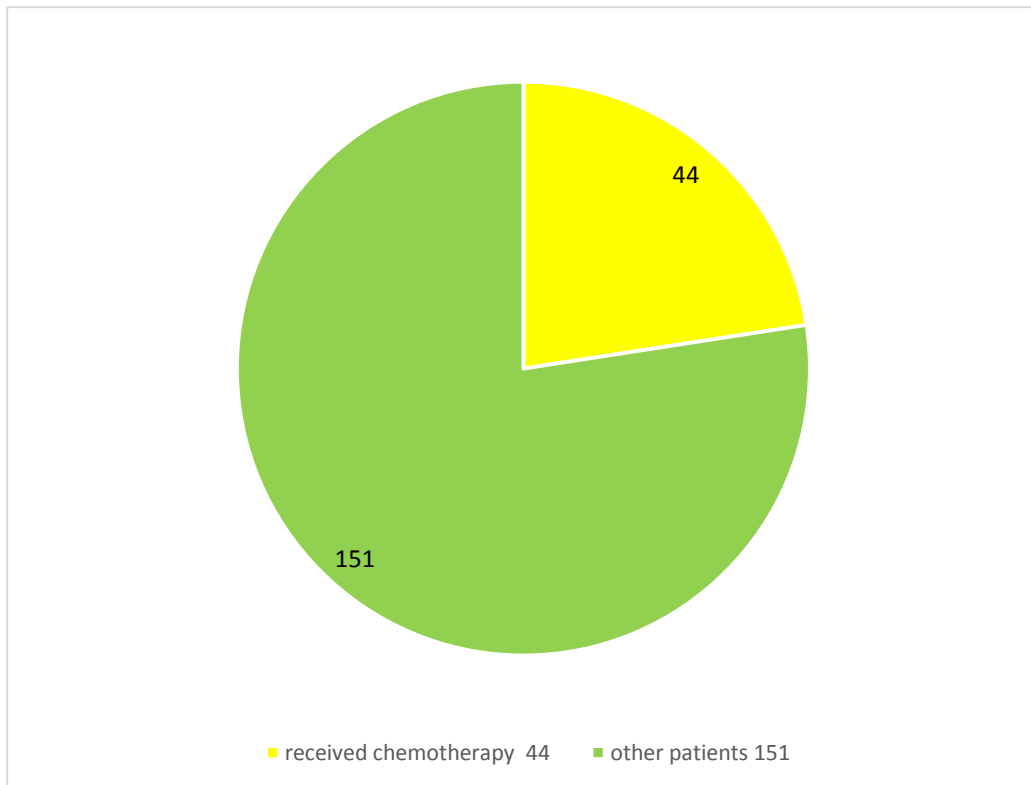


## RESULTS;

In patients receiving CT+RT + surgery at the end of 1 yr was (97%) 3 yr (80%) 5yr(70%) 10 yr,(71%).

## CHEMOTHERAPY

Out of 195 patients with Metastatic Breast Cancer  
44 patients received chemotherapy alone.



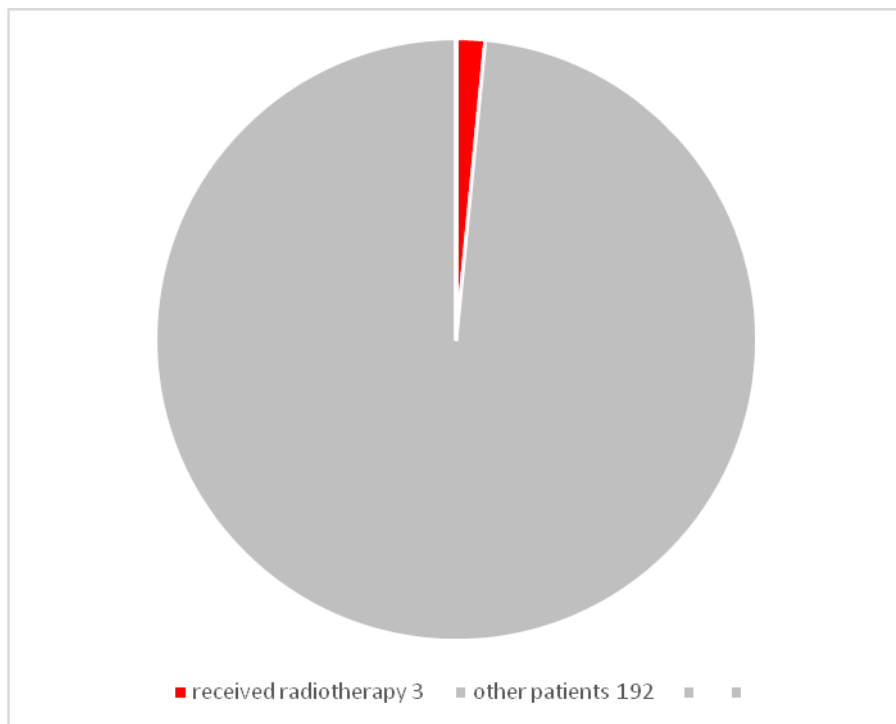
## RESULTS

In patients receiving CT only at the end of 1 yr was (60%) 3 yr (5%) 5yr(2%) 10 yr,(0%).



## **RADIOTHERAPY**

Out of 195 patients with Metastatic Breast Cancer 3 patients received radiotherapy alone.

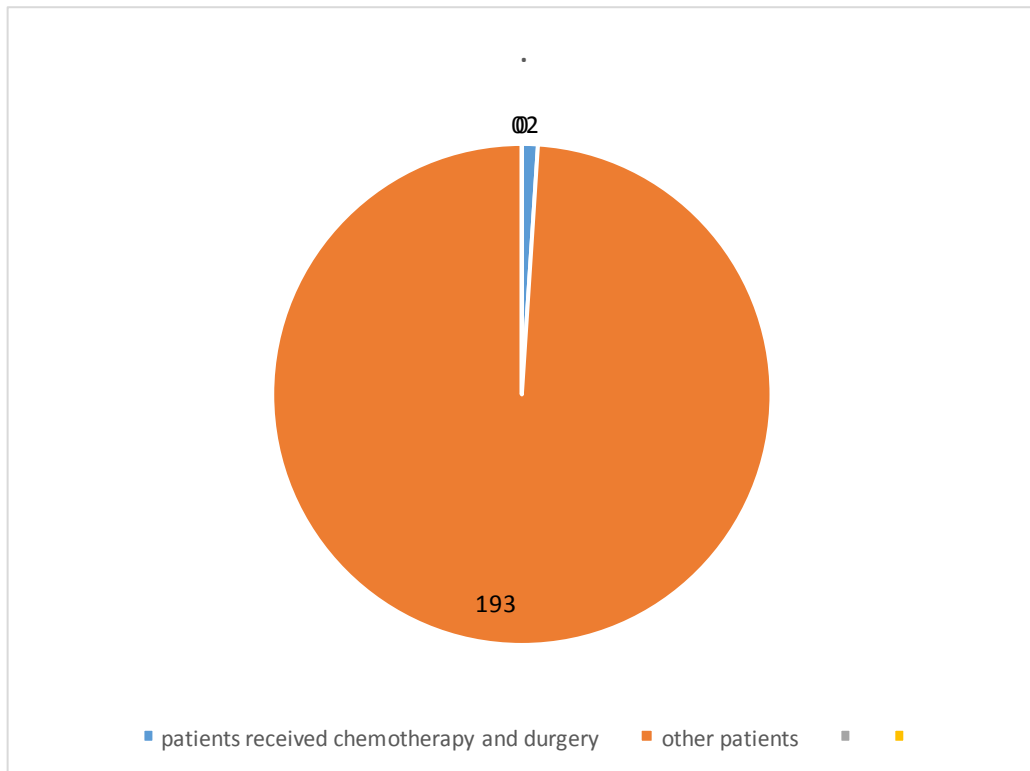


## **RESULTS:**

In patients receiving RT only at the end of 1 yr was (67%) 3 yr (33%) 5yr(33%) 10 yr,(33%).

## CHEMOTHERAPY AND SURGERY

OUT OF 195 PATIENTS RECEIVED chemotherapy and surgery



## Hormonal therapy

8 patients received hormonal therapy alone.

12 patients got chemotherapy and hormonal therapy

5 patients received radiotherapy and hormonal therapy.

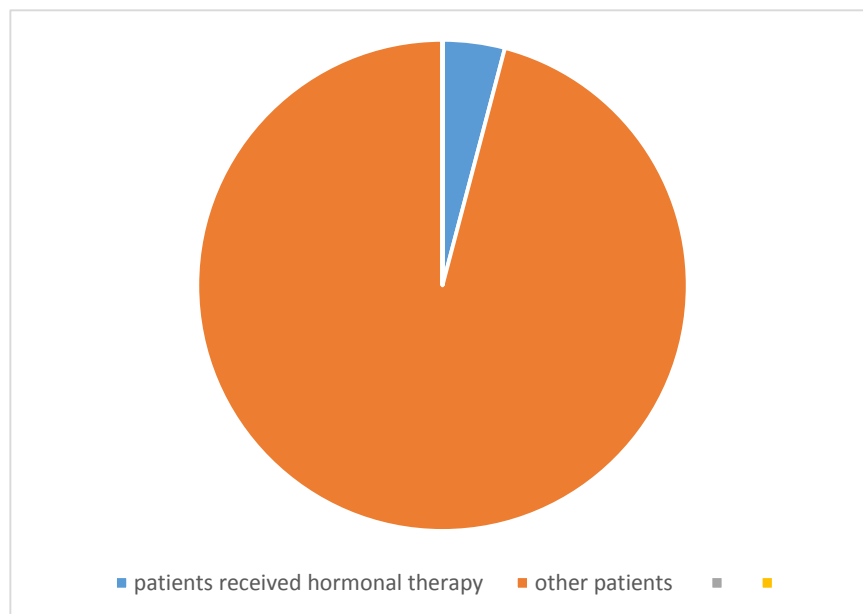
6 patient sreceivedhemoirradiation and hormonal therapy

NO OF PATIENTS	195
HT	8
CT+HT	12
RT+HT	5
CT+RT+HT	6

## HORMONAL THERAPY

Out of 195 patients with Metastatic Breast Cancer

8 patients received hormonal therapy alone.

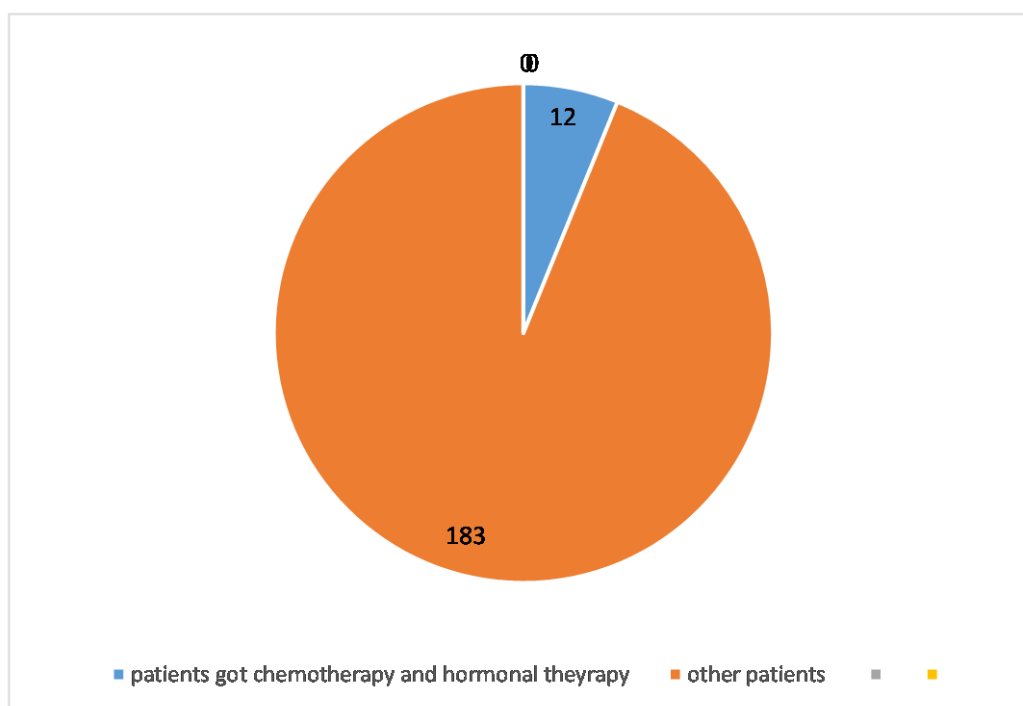


In patients receiving HT only at the end of 1 yr was (50%)

3 yr (13%) 5yr (13%) 10 yr,(13%).

## Chemotherapy and hormonal therapy

Out of 195 patients with Metastatic Breast Cancer 12 patients got chemotherapy and



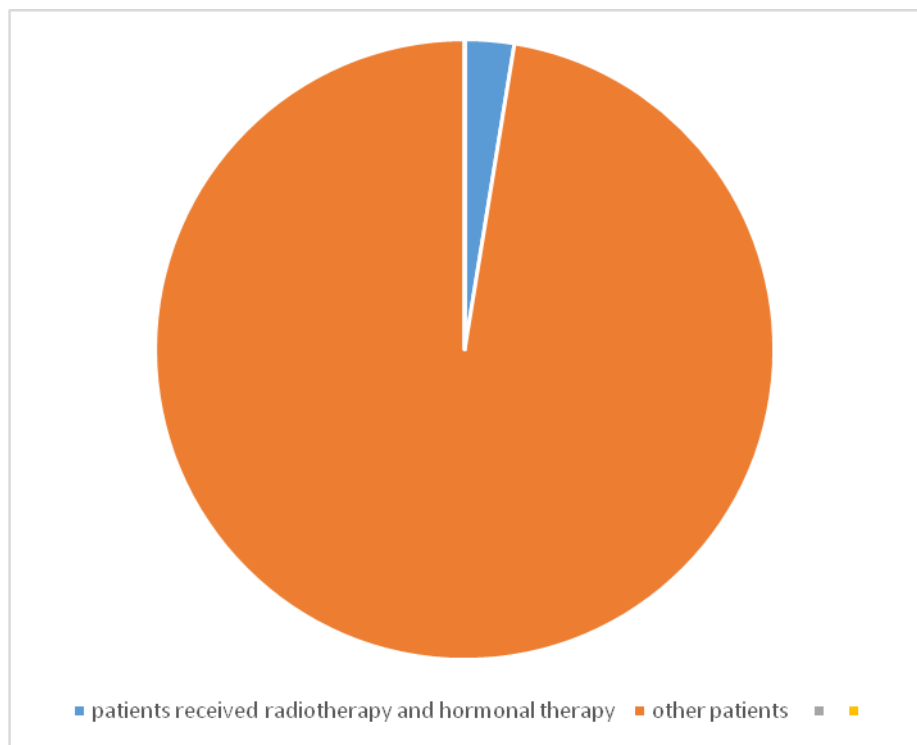
hormonal therapy

In patients receiving CT+HT at the end of 1 yr was (58%) 3yr (8%) 5yr(0%) 10 yr,(0%).

## Radiotherapy and hormonal therapy

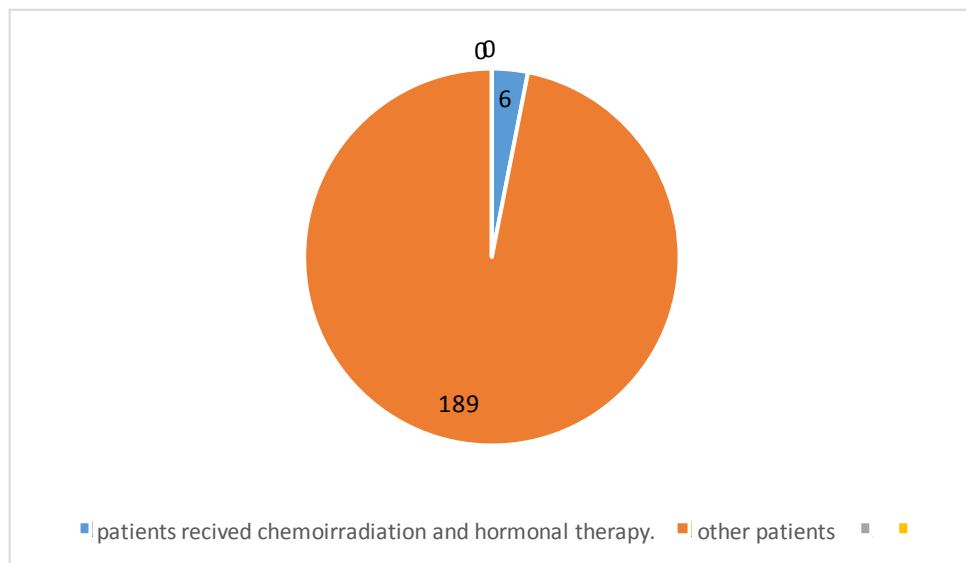
Out of 195 patients with Metastatic Breast Cancer

5 patients received radiotherapy and hormonal therapy



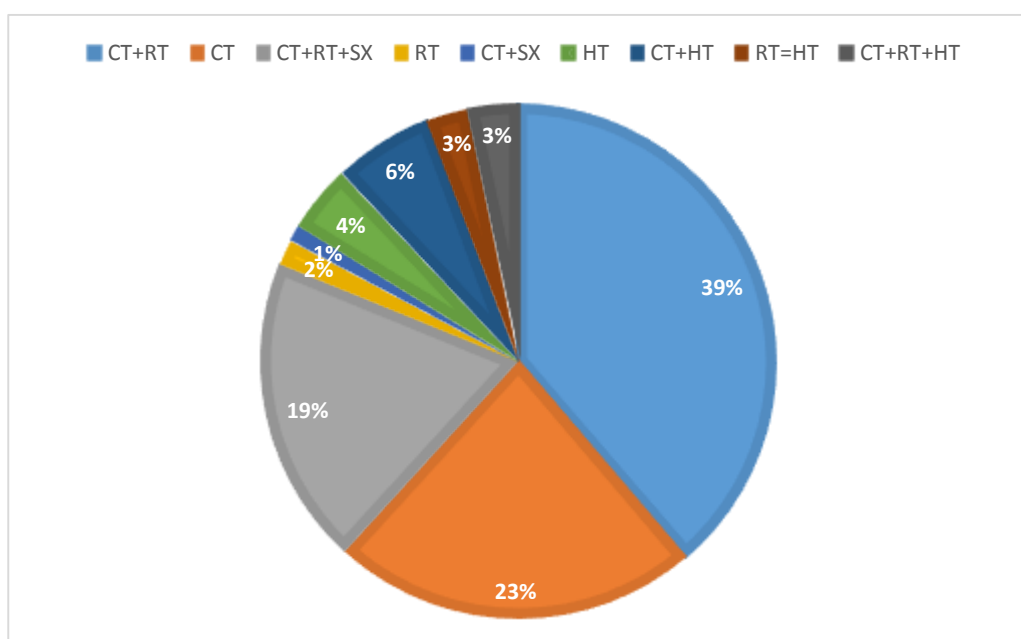
In patients receiving RT + HT at the end of 1 yrsurvival was (50%) 3yr(0%) 5yr(0%) 10 yr,(0%).

Chemoirradiation and hormonal therapy. Out of 195 patients with Metastatic Breast Cancer 6 patientsreceived Chemoirradiation and hormonal therapy.



In patients receiving CT+RT + HT survival at the end of 1 yr was (67%)  
 3yr(50%) 5yr(0%) 10 yr,(0%).

## VARIUOS TREATMENT MODALITIES



FACTOR	NO OF CASES	SURVIVAL PERCENTAGE			
		1 yr	3 yr	5 yr	10 yr
Treatment modality					
0	4	50	25	25	0
2	72	89	58	46	42
3	1	100	100	100	100
5	35	97	80	77	71
6	43	60	5	2	0
7	3	67	33	33	33
8	8	50	13	13	13
9	12	58	8	0	0
10	4	50	0	0	0
11	6	67	50	0	0

2vs 5=p value< 0.005

2vs 3=p value< 0.308

2vs 6=p value< 0.001

5vs 6 =p value<0.001

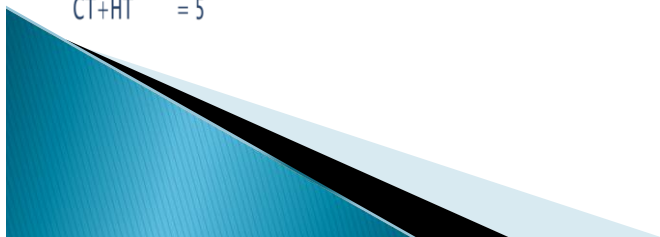
CT+RT+SX = 5

CT+RT = 2

CT+SX = 3

CT = 5

CT+HT = 5



V Out of 195 patients 74 patients received chemoradiation and then underwent surgery.

FACTOR	NO OF CASES	SURVIVAL PERCENTAGE			
		1 yr	3 yr	5 yr	10 yr
All cases	188	78	43	35	30
Pre Menopause	65	77	43	35	26
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ER negative	55	75	40	36	34
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1vs 3=p value< 0.003  
 1vs 6=p value< 0.001  
 1vs 8=p value< 0.024  
 2vs 3 =p value<0.008  
 2vs 6=p value< 0.001  
 4vs 6=p value< 0.043

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9	12	58	8	0	0
10	4	50	0	0	0
11	6	67	50	0	0

2vs 5=p value< 0.005  
 2vs 3=p value< 0.308  
 2vs 6=p value< 0.001  
 5vs 6 =p value<0.001

CT+RT+SX = 5  
 CT+RT = 2  
 CT +SX = 3  
 CT = 5  
 CT+HT = 5



## **Discussion**

The purpose of the study was to evaluate the role of locoregional treatment in metastatic breast cancer since this was a retrospective study between the year of 2003 – 2008 all medical records of female metastatic breast cancer patients excluding brain metastasis were revised and analysed with a following factors such as menopausal status, hormone receptor status, HER2 neu status, no of metastasis (including visceral and non-visceral)

65 patients in this study were premenopausal and 112 patients were belonged to postmenopausal group 55 patients were ER negative and 84 patients were ER positive and out of 195 patients 14 patients were HER2 positive and 31 patients were HER2 negative and in the remaining cases status not known.

31 patients had single bone metastasis and 68 pts had multiple bone metastasis 18 patients had liver metastasis and 21 patients had lung metastasis 2 patients had metastasis liver and lung 3 patients with supraclavicular metastasis 7 patients had axillary metastasis.

All patients underwent various treatment modalities according to tumour board policy. 74 patients underwent chemo radiation 2 patients had chemotherapy followed by surgery 37 patients got concurrent chemo radiation followed by surgery. 44 patients received chemotherapy alone. 3 patients had only radiotherapy 12 patients received chemotherapy and harmonic therapy 8 patients had harmonic therapy only in 5 patients radiotherapy and harmonic therapy was given 6 patients had chemo radiation followed by hormonal therapy.

Patients survival was analysed at the end of 1 yr, 3 yr, 5 yr, and 10 years. In patients receiving CT+RT survival at the end of 1 yr was (89%) 3 yr (58%) 5 yr (46%) 10 yr,(42%). In patients receiving CT+RT + surgery at the end of 1 yr was (97%) 3 yr (80%) 5yr(70%) 10 yr,(71%). In patients receiving CT only at the end of 1 yr was (60%) 3 yr (5%) 5yr(2%) 10 yr,(0%). In patients receiving RT only at the end of 1 yr was (67%) 3 yr (33%) 5yr(33%) 10 yr,(33%). In patients receiving HT only at the end of 1 yr was (50%) 3 yr (13%) 5yr (13%) 10 yr,(13%).

In patients receiving CT+HT at the end of 1 yr was (58%) 3yr (8%) 5yr(0%) 10 yr,(0%). In patients receiving RT + HT at the end of 1

yr was (50%) 3yr(0%) 5yr(0%) 10 yr,(0%). In patients receiving CT+RT + HTat the end of 1 yr was (67%) 3yr(50%) 5yr(0%) 10 yr,(0%).

## **Conclusion**

The data reported in this retrospective study confirmed that chemo-radiation improved overall survival and symptomatic local control were demonstrated in locoregionally treated patients with metastatic breast cancer. The optimal local management of patients with metastatic breast cancer remains unknown. An ongoing phase III trial, E2108, has been designed to assess the effect of locoregional management in metastatic patients responding to first-line systemic therapy. Loco regional radiation can be an integral part in metastatic breast cancer treatment to improve the quality of life. If the patient did not have any metastasis at the end of one year mastectomy can be added to still more improve the local control according to this study as there is a significant overall survival and better local control with concurrent chemo radiation hence RT has a integral part in the management of metastatic breast cancer.

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